Herbs & Natural Supplements

An evidence-based guide 3RD EDITION

Lesley Braun
Marc Cohen

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 indicates a herb or supplement action with particular significance for pregnant women.

 indicates a warning or cautionary note regarding the action of a herb or supplement.

 indicates FAQs about the herb or supplement.

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CONTENTS

Appendixes

ORGANISATION OF THIS BOOK

This third edition of *Herbs & natural supplements – an evidence-based guide* is organised into four sections. The first section provides a basic introduction to complementary medicine in general and then, more specifically, to herbal medicine, clinical nutrition, aromatherapy, and food as medicine. It is hoped that many of your general questions will be answered here.

The second section focuses on issues relating to clinical practice and explores the relatively new fields of integrative medicine and wellness, as it relates to health. These areas are gaining popularity around the globe and complementary medicine philosophy and treatments are often an integral part of the approach. This section also contains chapters with a focus on safety because the wise clinical use of all interventions must be based on a benefit versus risk assessment. There are general chapters discussing the safety of herbs and natural supplements and drug interactions, and then specific chapters focusing on safety in pregnancy, before surgery and for people undertaking treatment for cancer. These topics are discussed in both a theoretical and a practical way to clarify the key concerns and produce some general guidelines that can be used to inform practice.

The third and largest section comprises 130 evidence-based reviews of some of the most popular herbs and natural supplements available over the counter. Exhaustive reviews of the peer-reviewed literature have been undertaken by the author team to update, modify and expand information from the previous edition, and 10 new monographs are included. Common names, chemical components, main actions, clinical uses, dosage range and safety issues are included for each herbal medicine. For nutritional supplements, background information and pharmacokinetics, food sources, deficiency signs and symptoms and the new Australian and New Zealand recommended daily intakes (RDIs) are also included where appropriate. Although technical language is frequently used, there is also a summary in non-technical language (Practice Points and Patient Counselling) and answers to key questions patients may have about the product (Patients' FAQs). A 'Historical note' is included where appropriate and occasionally there are also 'Clinical note' boxes that provide further information.

The fourth section consists of ready-reference appendices, the largest of which is a table that outlines the interactions possible between the 130 complementary medicines reviewed and pharmaceutical drugs (Appendix 2). Although investigation into this area is still in its infancy, we have provided a brief explanation for each possible interaction and a general recommendation based on what is currently known or suspected. It is intended as a guide only, to be used to inform practice when clinicians take a medical and medication history: obviously it should be interpreted within the individual patient's context. It is anticipated that this section will continue to change in future editions as more clinical studies are published and theoretical predictions are tested. Appendix 5 is a guide to the safe use of complementary medicines in the preoperative period. Appendix 7 is a table organised by pharmacological action giving the herbs and nutrients that produce that action and the type of evidence available to support this. For example, to find which herbs and nutrients exert an anti-inflammatory action, check under 'Anti-inflammatory'. We have also included a glossary of medical, research, integrative and complementary medicine terms and abbreviations (Appendix 1), a list of Australian and New Zealand poisons information centres and their phone numbers (Appendix 3), and the contact details for teaching institutions, complementary and integrative medicine associations and product manufacturers in Australia and New Zealand (Appendix 4). These lists are not exhaustive but aim to provide a general guide for the reader.

ACKNOWLEDGMENTS

This third edition of *Herbs and Natural Supplements* is bigger than the second edition, which in turn was much bigger than the first. This is partly because 10 new monographs and two new chapters have been added, but also because the amount of published research in complementary medicine is still growing exponentially and there are now over 40,000 articles cited on Medline alone in this area.

The task of amassing, critiquing and reporting on the plethora of complementary medicine studies available is a daunting one that requires dedication, tenacity, patience and resourcefulness. This edition draws on the expertise of an expanded team of 12 contributors. I believe they are among the brightest and most talented CM writers in Australia. Without their valuable involvement, this book might never have been completed.

On a personal note, I'd like to thank my husband Gary for making it possible for me to step aside from our busy lives for many months to sit, think and write, while he took on the main family responsibilities. This work requires a lot of mental energy and introspection, which means retreating from the details of daily routine so it can all happen. His understanding, motivation and patience are invaluable and always greatly appreciated.

I'd also like to thank all my parents Shana and Fred Green, Judy Braun and Magenesta and Zonti Kustin for their emotional and hands-on support; my late father-in-law Emil Braun and grandfather Leon Kustin, who continue to serve as reminders to have courage and persevere; and the rest of my wonderful extended family and friends who accept that I'm off the radar every now and again, working on another book.

I'd like to thank contributing writers Liza Oates, Rachel Arthur, Jane Daley and Trisha Dunning, who have stayed on the ride for this edition and continue to share their valuable expertise. Thank you also to Marc Cohen, who remains a visionary, and to new team members Ondine Spitzer, Gina Fox, Evelin Tiralongo, Louise Zylan, Leah Hechtman, Emily Bradley, Clare Francis and Surinder Baines for their commitment and professionalism.

I'd also like to thank Professor Franklin Rosenfeldt, who inspires me every day at the Alfred Hospital, colleagues at the National Herbalists Association of Australia (NHAA), colleagues in the Alfred Hospital pharmacy department, Steven Chong at the Journal of Complementary Medicine, Matthew Eton at the Australian Journal of Pharmacy, fellow practitioners, academics and researchers (in all the health fields) and, of course, patients. At Elsevier, I'd like to thank everyone involved in this project for making it as seamless as possible.

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Lesley Braun
Melbourne, Australia
2009

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Dr Lesley Braun is a registered pharmacist and naturopath. She holds a PhD from RMIT University, Melbourne, Australia, in which she investigated the integration of complementary medicine into hospitals in Victoria. She is currently Research Fellow in the Cardiothoracic Surgical Research Unit at the Alfred Hospital (Department of Surgery, Monash University), where she conducts clinical trials using integrative medicine in the hospital setting, supervises research students and is involved in the National Institute of Complementary Medicine Collaborative Centre for Natural Medicines and Neurocognition. Her other role at the Alfred hospital is as Research Pharmacist in the Pharmacy Department, where her work focuses on complementary medicine products and the practice of integrative medicine within pharmacy settings.

Dr Braun is also Vice President of the National Herbalists Association of Australia, a member of the Therapeutic Goods Administration's (TGA) Complementary Medicine Evaluation Committee (CMEC), an advisory board member to the Australasian Integrative Medicine Association (AIMA), on the editorial board of the Journal of Complementary Medicine (JCM), a member of several advisory committees for the National Institute of Complementary Medicine (NICM), on the academic board of the Endeavour College of Natural Health and a member of several complementary medicine working groups for the Clinical Oncology Society of Australia (COSA).

Since 1996 she has authored numerous chapters for books and more than 100 articles, and since 2000 has written regular columns for the *Australian Journal of Pharmacy* and the *Journal of Complementary Medicine*. She lectures to medical students at Monash University and to chiropractic students at RMIT University, and is regularly invited to present at national and international conferences about evidence-based complementary medicine, drug interactions and complementary medicine safety.

Her role as the main author of *Herbs and Natural Supplements — An Evidence-based Guide* represents a continuation of a life-long goal to integrate evidence-based complementary medicine into standard practice and improve patient outcomes safely and effectively.

Professor Marc Cohen MBBS(Hons), PhD(TCM), PhD(Elec Eng), BMedSc (Hons), FAMAC, FICAE

Marc Cohen is currently Professor of Complementary Medicine at RMIT University, where he leads the world's first online postgraduate Master of Wellness program, supervises postgraduate research students and conducts research funded by the National Health and Medical Research Council and other agencies into various aspects of wellness and complementary medicine. He is also Senior Research Fellow at the Centre for Medical and Health Sciences Education, Monash University, Expert Advisor to the Therapeutic Goods Administration's (TGA) Complementary Medicine Evaluation Committee (CMEC), a member of the Scientific Advisory Committee for the National Institute of Complementary Medicine (NICM), a current Board Member and Past-President (President 2000–2007) of the Australasian Integrative Medicine Association (AIMA) and a member of the Royal Australian College of General Practitioners (RACGP)/AIMA Joint Working Party, which has guided the development of the RACGP curriculum on integrative medicine.

Professor Cohen is a registered medical practitioner with degrees in Western medicine, physiology and psychological medicine, as well as PhDs in both Chinese medicine and biomedical engineering. He sits on the

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CHAPTER 1
INTRODUCTION TO COMPLEMENTARY MEDICINE

The practice of medicine aims to reduce human suffering through the treatment and prevention of disease, and has been part of every human society and civilisation throughout history. Although medicine has a single aim, over the ages many different practices and techniques have evolved to achieve this. We are currently living at a time when the wisdom of many different cultures and philosophies is available to us as never before. Despite the existence of a wide range of therapies, medicine in the Western world has been largely institutionalised and dominated by the scientific biomedical model that centres on treating disease with drugs and surgery. In more recent times a new model has started to emerge; it attempts to integrate some of those therapies and medicines that are not based on the biomedical model and that have been previously termed 'alternative'. Although still in its infancy, integrative medicine, as some have called it, views 'alternative medicine' as complementary to the existing system and seeks to improve and enlarge the scope of the existing biomedical model.

WHAT IS COMPLEMENTARY MEDICINE?

The definition of complementary and alternative medicine (CAM) has been the subject of some debate. In 1995 the following definition was formulated at a conference held by the National Institutes of Health's Office of Alternative Medicine in the USA, with the aim of producing a definition that has the broadest and most consistent applicability and that excludes bias and partisanship:

> Complementary and alternative medicine (CAM) is a broad domain of healing resources that encompasses all health systems, modalities, and practices and their accompanying theories and beliefs, other than those intrinsic to the politically dominant health system of a particular society or culture in a given historical period. CAM includes all such practices and ideas self-defined by their users as preventing or treating illness or promoting health and well-being.
>
> *National Institutes of Health Panel on Definition and Description 1997*

Like many definitions produced by committees, this definition seems a little unsatisfying. Simply dividing interventions into those that are part of the politically dominant health system and those that are not does not provide useful insight. This classification is also subject to regional political differences that may be unrelated to healthcare.

Rather than focus on political acceptance as the basis for defining alternative and complementary medicine, a discussion paper by the Australian Medical Council addresses 'unorthodox therapies' and states that 'the practices they embrace are by definition unscientific and of unproven efficacy until proved otherwise (in which case they become part of mainstream medicine)' (Australian Medical Council, 'Undergraduate medical education and unorthodox medical practice', unpublished discussion paper, 1999).

The division of therapies into unorthodox or mainstream based on scientific merit is a little simplistic and open to subjective interpretation. For example, there are many practices that can be considered mainstream but are not necessarily scientifically proven, and many practices that can be considered 'unorthodox'

but have scientific support. Furthermore, scientific evidence for a therapy may exist for only a specific clinical condition, or a therapy may be considered orthodox in one context, such as the use of vitamin supplements for treating a deficiency syndrome, but unorthodox in another, such as the use of vitamins in megadoses.

When defining therapies on political or scientific grounds, further confusion is added by the time that it takes to gain wide acceptance. For example, even though scientific evidence in support of acupuncture has been accumulating since the discovery of endogenous opioids in the mid-1970s, and government rebates via Medicare have been available for acupuncture for nearly two decades, this therapy is not universally accepted as mainstream.

Overall, it is generally accepted that there are two broad classes of medicine, and terms such as 'conventional', 'mainstream', 'orthodox', 'biomedicine' and 'scientific medicine' are often contrasted with 'unconventional', 'complementary', 'alternative', 'unorthodox' and 'fringe medicine'. Perhaps the most common distinction is between 'conventional' and 'complementary' therapies, yet these terms seem to defy precise definition. Even so, complementary medicine generally refers to the use of interventions that complement the use of drugs and surgery. The range of such therapies is vast and includes treatments based on traditional philosophies, manual techniques, medicinal systems, mind–body techniques and bioenergetic principles (Table 1.1). These techniques vary widely with respect to levels of efficacy, cost, safety and scientific validation, yet they often share common principles, including the concept of supporting the body's homeostatic systems, as well as acknowledging the role of lifestyle practices, personal creativity, group sharing, the mind–body connection and the role of spiritual practice in health.

COMPLEMENTARY MEDICINE IN AUSTRALIA

The practice of complementary medicine is flourishing in Australia. In 2000 it was estimated that about 50% of the Australian population took a 'natural supplement', about 20% formally saw a complementary medicine practitioner, and public spending on complementary medicines (A$2.3 billion in 2000) was more than four times patients' contributions for all pharmaceutical medications (MacLennan 2002). A follow-up survey performed in 2004 found that although spending on complementary medicines had decreased to A$1.8 billion, there was a slight increase in the number of people taking natural supplements and visits to complementary medicine practitioners rose to 26.5% (MacLennan et al 2006). More recent statistics reveal that up to 70% of the Australian population has used complementary medicine in a number of different forms (Xue et al 2007). Data from the Australian Bureau of Statistics indicates that in the 10 years leading up to 2006, the number of people visiting CM practitioners within a 2 week period rose from approximately 500,000 to 750,000 and over the same period there was an 80% increase in the number of people employed as a CM practitioner. The most commonly consulted CM practitioners were chiropractors, naturopaths and acupuncturists (Censuses of Population and Housing and from the ABS 2004-05 National Health Survey).

These figures are comparable to those from the USA, which further suggest that the use

TABLE 1.1 The Range of Complementary Therapies

Philosophical systems	Medicinal	Bioenergetic
• Ayurvedic	• Herbal therapies	• Magnetism
• Yoga	• Homeopathy	• Pulsed electromagnetic fields
• Traditional Chinese medicine	• Diet modification	• Qi gong
• Shamanic healing	• Nutritional supplementation	• Reiki
• Naturopathy	• Aromatherapy	• Therapeutic touch
Mind–body	**Manual**	
• Meditation	• Chiropractic	
• Hypnosis	• Massage	
• Self-help/support groups	• Reflexology	
• Biofeedback	• Shiatsu	
• Prayer/spiritual healing	• Osteopathy	

of CAM is increasing. Between 1990 and 1997 expenditure on these therapies in the USA increased by 45.2%, with the total of more than US$21 billion exceeding out-of-pocket expenditures for all US hospitalisations. Furthermore, visits to CAM practitioners exceeded total visits to all US primary-care physicians (Eisenberg 1998).

Similarly, use of complementary therapies by general practitioners seems to be increasing. Recent surveys have estimated that 30–40% of Australian GPs practise a complementary therapy and more than 75% formally refer their patients for such therapies (Cohen et al 2005, Hall 2000, Pirotta 2000). It is also estimated that more than 80% of GPs think it appropriate to practise therapies such as hypnosis, meditation and acupuncture and that most GPs desire further training in various complementary therapies (Cohen et al 2005, Pirotta 2000).

Interestingly a recent survey of Australian GPs found that, based on their opinions, complementary therapies could be classified as follows: non-medicinal and non-manipulative therapies such as acupuncture, massage, meditation, yoga and hypnosis, which GPs considered to be highly effective and safe; medicinal and manipulative therapies, including chiropractic, Chinese herbal medicine, osteopathy, herbal medicine, vitamin and mineral therapy, naturopathy and homeopathy, which more GPs considered potentially harmful than potentially effective; and esoteric therapies such as spiritual healing, aromatherapy and reflexology, which were seen to be relatively safe yet also relatively ineffective. Furthermore, according to GPs the risks of complementary therapies were seen to arise mainly from incorrect, inadequate or delayed diagnoses and interactions between complementary medications and pharmaceuticals, rather than the specific risks of the therapies themselves (Cohen et al 2005).

The interest of GPs in CAM is supported by the forming of links between the Australasian Integrative Medicine Association and the Royal Australian College of General Practitioners with the release of a joint position paper on complementary medicine (RACGP/AIMA 2005), as well as the introduction of teaching of CAM in undergraduate medical courses. Further academic support is evident by the establishment of departments of complementary medicine at respected universities and a proliferation of peer-reviewed journals documenting the growing body of rigorous research in the field. In line with these developments, the status of complementary medicine practitioners has been elevated, with the establishment of degree courses in natural medicine and formal registration of some professions.

There appear to be many reasons for the popularity of complementary medicine. Certainly, orthodox medicine does not have a monopoly on cure and, despite its effectiveness in treating trauma and acute disease, when it comes to chronic illness there are many people in the community who continue to suffer despite its best efforts. The public are also demanding greater autonomy and involvement in their own healthcare, and want to prevent or slow down ageing and achieve higher levels of functioning. Additionally, the exponential increase in scientific studies being published on complementary medicine therapies has no doubt added to the public's interest and confidence in its use.

Although interest in CAM has increased among both practitioners and patients, this has been paralleled by increased support from the federal and state governments. In Australia this has been demonstrated by the granting of degree status to schools of natural medicine, the exemption of some complementary therapies from the Goods and Services Tax, and government support for private health insurance companies, many of which cover complementary medicine. The federal government has also provided these therapies with formal recognition by establishing an Office of Complementary Medicine as part of the Therapeutic Goods Administration and the Complementary Medicine Evaluation Committee (CMEC), and the Victorian Government is the first outside of China to regulate the practice of traditional Chinese medicine (TCM). From the viewpoint of government spending, this encouragement makes fiscal sense, as natural therapies do not attract Medicare benefits and spending on complementary medicines is patient- rather than government-funded.

Despite moves to support complementary therapies, in practice it seems that there are two distinct healthcare systems operating in parallel, and interaction is still in its infancy. It is estimated that, of the patients who go to complementary practitioners, more than 57% do not inform their doctor they are doing so (MacLennan et al 2006). This lack of communication is potentially hazardous, as it raises the possibility of treatment interactions; this is even more significant when it is considered that in the USA more than 80% of people

seeking complementary treatment for 'serious medical conditions' were found to be receiving treatment from a medical doctor for the same condition (Eisenberg 1993).

COMPLEMENTARY MEDICINE IN NEW ZEALAND

Complementary medicine has been practised in New Zealand since the 19th century (Duke 2005). In 1908, the Quackery Prevention Act was enacted to prevent the sale of dubious medicines or medical devices and represents an early attempt to regulate the practice of CAM. At the time, what is now termed CAM had achieved a level of acceptance among the medical profession; however, a division began to emerge between medical and complementary practices because of the Act.

Over the past decade, studies indicate that conventional medical practitioners in New Zealand practise some form of complementary therapy or refer their patients to complementary medicine practitioners (Duke 2005). One study of 226 GPs in Wellington suggested that they saw their role as ranging from comprehensive provider of both conventional and complementary medicine to selective practitioner of some options (Hadley 1988). Of these GPs, 24% had received complementary medicine training, 54% wanted further training in a complementary therapy, and 27% currently practised at least one therapy. The study also found that acupuncture, hypnosis and chiropractic were the most popular therapies among this group.

In June 2001, the Ministerial Advisory Committee on Complementary and Alternative Health (MACCAM) was established in order to advise the New Zealand Minister of Health. Policies regarding regulation, consumer information needs, research evidence and efficacy and integration were investigated, together with a range of strategies to allow CAM to contribute to the mainstream objectives of the New Zealand Health Strategy (MACCAM 2004).

Currently, the New Zealand Charter of Health Professionals estimates that there are 10,000 CAM practitioners nationally. The 2002–03 New Zealand Health Survey (n = 12,000) indicated that approximately 24% of adults had visited a CAM practitioner over the 12-month study period (MACCAM 2004). Massage therapists, chiropractors, osteopaths, homeopaths or naturopaths were the most commonly consulted CAM practitioners. The survey found that 32.5% of people seeing CAM practitioners did so for the treatment of a chronic condition, long-term illness or disability, while 33% also saw a GP for the same condition. A belief that CAM practitioners can provide help with conditions that other healthcare professionals are unable to treat was the main driving force behind their choice. Most referrals came from friends; however, 12% reported that they had been referred to the service by a medical doctor.

THE MEDICAL SPECTRUM

The range of available therapies is vast, but there is a common benchmark for all — reducing human suffering. On this criterion, it is possible to classify all medicine into good and bad, with good medicine defined as effective, safe, practical and, ideally, evidence based, and bad medicine defined as ineffective or potentially harmful.

Additionally, the different therapies can be seen to exist across a spectrum with multiple dimensions, such as safety, efficacy, practicality, availability, utility and cost-effectiveness. At one end of this spectrum is the science of medicine, which aims to understand and combat the disease process from a pathophysiological perspective. Therapies using this approach are often at the core of mainstream medicine, require practitioner intervention, target a specific organ, system, tissue or biochemical process, and are usually subsidised by the public purse. At the opposite end is the art of medicine, which aims to support the body's homeostatic processes to facilitate healing and enhance the subjective sensation of wellness. Therapies using this approach often involve philosophical systems with a spiritual dimension, are highly individualised, consider the whole person and may require significant patient involvement and cost. When considering the different dimensions of medical practice, it becomes clear that best practice should incorporate both approaches and combine the art and science of medicine.

Health and disease can also be considered to inhabit opposite ends of an illness–wellness spectrum, with health being classified into three broad areas — ill-health, average health and enhanced health (Figure 1.1) (see also Chapter 12). In the past, Western medicine has focused on helping people move from ill-health to average health and has viewed the

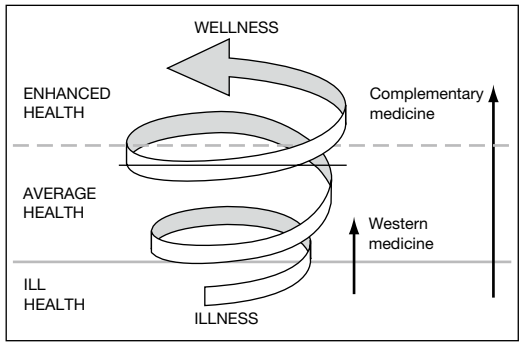

FIGURE 1.1 Conceptualisation of the spectrum of health

absence of disease as an ideal goal. In relatively recent times, preventative treatment has also been incorporated into medical management, in an attempt to reduce the incidence or exacerbation of disease states. In comparison, CAM has always maintained a focus on preventative approaches and moving people from average health to a state of enhanced health. In Eastern medicine there is a concept of a 'perfect health' state, in which a person is totally balanced and 'at one with the universe', and hence in a state of perpetual bliss or 'nirvana'.

INTEGRATIVE AND HOLISTIC MEDICINE

When complementary and conventional approaches to medicine are combined, their practice is often called holistic or integrative medicine (see Chapter 6). This combined approach aims to achieve a balance between art and science, theory and practice, mind and body, and prevention and cure. The practice of integrative medicine is highly individualised and focuses on *how* medicine is practised rather than the use of any particular modalities. It embraces a philosophy that adheres to certain principles, such as the BEECH principles:

- **B** **B**alance between complementary aspects
- **E** **E**mpowerment and self-healing
- **E** **E**vidence-based care supporting the concept 'First, do no harm'
- **C** **C**ollaboration between practitioner and patient, and between different practitioners
- **H** **H**olism and the recognition that health is multidimensional.

Integrative medicine focuses on patient self-healing and empowerment through education and health promotion, and aims for a collaborative approach through a partnership model. Overall, an evidence-based, patient-centred care approach is adopted that includes the fundamental principle of *primum non nocere* or 'First, do no harm'. This approach considers the best available evidence on safety and efficacy, and recognises that each person is an individual whose health involves physical, psychological, social, spiritual and environmental dimensions. Integrative medicine also recognises that optimal healthcare requires a multidisciplinary approach, with each discipline having its own defined strengths, weaknesses and limitations.

Besides the use of disease-specific treatments, integrative medicine also incorporates general health-enhancing and supportive interventions to improve wellbeing. This may include stress management techniques such as meditation and relaxation training, exercise programs to improve physical activity, dietary recommendations to improve nutritional status, and education to provide a greater sense of control and understanding of illness and health. These interventions form the pillars of a holistic approach to healthcare and can be summarised by the SENSE approach:

- **S** **S**tress management
- **E** **E**xercise
- **N** **N**utrition
- **S** **S**ocial and spiritual interaction
- **E** **E**ducation

HERBAL MEDICINES AND NATURAL SUPPLEMENTS

Since the beginning of time, humans have sought to ease pain, heal sickness and improve energy levels by using various substances as medicines. These attempts began by using things found in the local environment, such as plants, minerals and animal parts, and has now evolved to include many previously unknown chemical entities, such as vitamins, minerals and phytochemicals. Today, an unprecedented range of herbal and natural supplements and functional foods is available.

As with all treatments, the benefits of using a medicine, changing a diet or making lifestyle changes must be weighed against the potential for doing harm: that is, the risk of using/taking/doing something and causing harm, or of not using/taking/doing it and causing harm (Table 1.2, p 6). Adverse effects from the use of natural supplements can result from an inherent property of the substance itself, inappropriate use, product adulteration or contamination not related to the substance but found within the preparation, and interactions with other substances or preexisting medical conditions.

TABLE 1.2 Reasons for Using Herbal Medicines and Natural Supplements	
Efficacy	When they will alleviate symptoms of disease, reduce exacerbation or present a cure.
Safety	When they present a safer treatment option than other therapies.
Cost	When they provide cost-effective treatment options.
Adjunct	If the efficacy and/or safety of other interventions can be improved with adjunctive use.
Prevention	When they provide safe prevention strategies in at-risk populations.
Enhance health	If they give a sense of improved wellbeing and quality of life.
Enlists	They involve patients in their own healthcare.

These issues are discussed in greater depth in the following chapters.

PRODUCT QUALITY AND REGULATION

Risk assessments are a key factor in the decision to use any intervention. Australia has an international best-practice, risk-based, regulatory system for both complementary and prescription medicines. This system is regulated by the Therapeutic Goods Administration (TGA), which aims to ensure safety, quality and truth in the labelling of therapeutic goods available to the Australian public. The TGA acts to control the supply of therapeutic goods, including complementary medicines, through three main processes — regulation of manufacturers, and pre- and post-marketing assessment and surveillance. These elements are supported by penalties for breaches of regulations.

The TGA acts to ensure that all therapeutic goods sold in Australia, including herbs and natural supplements as well as prescription medicines, are manufactured according to good manufacturing practice. It licenses manufacturers and conducts regular inspections to audit their compliance. High-risk products such as prescription medicines, or low-risk products with high-level claims, are individually evaluated for safety, quality and efficacy and are entered into the Australian Register of Therapeutic Goods (ARTG) as 'registered' goods, thereby carrying an 'AUST R' number on their labels. Low-risk products such as most herbs and natural supplements are evaluated only for safety and quality, 'listed' on the ARTG and then carry an identifying 'AUST L' number on their label.

Listed products are awarded low-risk status based on a number of controls, including assessment of the scientific evidence, the presence of label advisory information, dosage limits, mode of administration, restriction on the use of particular plant parts or other preparation restrictions, and container type. These products are able to carry a wide range of low- and medium-level medicinal claims, which must be supported by the appropriate level of evidence (Table 1.3). It should be noted that the levels of evidence designated by the TGA are slightly different from the levels designated by the National Health and Medical Research Council (NHMRC 1999), because the TGA acknowledges evidence from traditional use, accepting that, if a substance has been used with good effect and apparent safety for three generations, it may be considered safer than a newly created substance that has never existed in nature (TGA 2001).

In addition to regulating manufacturing and the control over label claims, the TGA also conducts post-marketing surveillance such as:

- monitoring of adverse drug reactions
- targeted and random laboratory testing of products and ingredients
- audit of good manufacturing practice
- an effective co-regulatory approach to controlling advertising of therapeutic goods. The Complementary Medicine Evaluation Committee (CMEC) is a ministerially appointed committee that advises the Office of Complementary Medicine within the TGA about matters relating to complementary medicine products.

Although Australia employs the same rigorous system for maintaining the quality of herbs and natural supplements as for prescription pharmaceuticals, this is not the case in many other countries. The problem of poor product quality has become a major concern in some Asian countries, where authorities have undertaken random sampling of suspected herbal products to determine whether adulteration has occurred. Huang et al (1997) report one survey in Taiwan where 2609 herbal samples were collected by eight major general hospitals. Analysis with thin-layer chromatography found an average of 23.7% of samples to be adulterated with chemical substances not stated on the label. Of these, more than half (52.8%) contained two or more adulterants (Awang 1996, Huang et al 1997).

TABLE 1.3 Levels of Evidence Used by the Australian TGA

Level of evidence	Type of evidence required
High-level scientific evidence	Evidence obtained from a systematic review of all relevant RCTs, without significant variations in the direction or degree of results. *OR* Evidence obtained from at least one properly designed randomised, controlled (preferably multicentre), double-blind trial. It is preferable to have data from at least two trials independent of each other, but in some cases, one large well-conducted trial may suffice (advice should be sought from the TGA in such cases).
Medium-level scientific evidence	Evidence obtained from well-designed controlled trials without randomisation. In the case of a homeopathic preparation, evidence from a well-designed, controlled homeopathic proving. *OR* Evidence obtained from well-designed analytical studies, preferably from more than one centre or research group, including epidemiological cohort and case–control studies. *OR* Evidence obtained from multiple time series with or without intervention, including within-country and between-country population studies. *Note:* In practice, the sources of most medium-level evidence will be peer-reviewed published papers and evidence-based reference texts. However, other evidence that meets the requirements, including independently reviewed unpublished evidence, may also be acceptable. Websites evaluating peer-reviewed published evidence may be a source of suitable evidence.
Low-level or general scientific evidence	Descriptive studies, case series or reports of relevant expert committees. Texts, such as TGA-approved pharmacopoeias or monographs, or other evidence-based reference texts, may be included in this level. Evidence derived from non-human data, such as in vitro studies and animal studies, and non-clinical studies, such as biochemical, nutritional and microbiological studies, does not stand alone and may be used only as supporting evidence.
Traditional evidence	Three or more generations of recorded use of a substance for a specific health-related or medicinal purpose that are documented by at least one of the following: • TGA-approved pharmacopoeia • TGA-approved monograph • three independent written histories of use in the classical or traditional medical literature • availability through any country's government public dispensaries • authenticated evidence of use from an oral tradition; modern texts that accurately report the classical or traditional literature may be used to support claims.

Source: TGA 2001

Government actions: the PAN Pharmaceuticals recall in Australia

On 28 April 2003 the TGA suspended the licence of Pan Pharmaceuticals, Australia's largest manufacturer of herbal, mineral and nutritional supplements at the time, and ordered the immediate withdrawal of hundreds of products it had manufactured. The company was accused of substituting ingredients, manipulating test results and having substandard manufacturing processes. The TGA was first alerted to possible manufacturing problems when dozens of adverse reaction reports to a pharmaceutical motion sickness tablet known as Travacalm were lodged. After some investigation, it was found that manufacture of this product was substandard and doses of the active ingredient varied enormously from that stated on the label.

Although the original product in question was a pharmaceutical drug, over the next few months media attention remained focused on natural medicine products, with some commentators seizing the opportunity to call into question the value of CAM in general. As a result, the Federal Government set up an expert committee to examine the role of complementary medicines in the healthcare system, including the supply of safe, high-quality complementary medicines, quality use of and timely access to these medicines, and the maintenance of a responsible and viable complementary medicines industry. The terms of reference set for this committee were very broad, not unlike those of the White House Commission on Complementary Medicine. The recommendations made by the expert

committee, which covered the regulation of complementary medicines and complementary healthcare practitioners, research, and the information and education needs of healthcare practitioners and consumers to improve community confidence in, and the viability of, the complementary medicines industry, could be viewed online at http://www.tga.gov.au/cm/cmreport2.htm, along with the government's response to these recommendations.

Following recommendations from this committee, and in recognition of the growing importance of complementary medicine in the Australian health system, the Federal Government established the National Institute for Complementary Medicine (NICM) in 2007. Its role was to provide leadership and support for complementary medicine research and the translation of evidence into clinical practice and policy, as well as to build research capacity and foster collaborations amongst researchers from different disciplines (see www.nicm.edu.au). NICM was provided with A$4.8 million for 2 years to achieve these goals. As part of its role in developing Australia's complementary medicine research capacity, NICM established three NICM collaborative research centres after a competitive submission process. The government's ongoing commitment to the future of NICM, however, remains uncertain.

What does seem certain, however, is that research into complementary medicine is likely to increase. The establishment of NICM coincides with the National Health and Medical Research Council making complementary medicine a priority area for research with over A$5 million of research funding being allocated to complementary medicine research in 2008. This has encouraged interdisciplinary collaboration, as many established researchers from other disciplines have become involved in funded projects in different areas of complementary medicine. Government recognition and support for complementary medicine in Australia seems to be paralleled around the world, although the level of funding support still lags far behind the United States. In 1992 the US government established the Office of Alternative Medicine with US$2 million funding. This office has now grown to become the National Centre for Complementary and Alternative Medicine (NCCAM) as part of the National Institute of Health (see http://nccam.nih.gov), with US$121 million in funding allocated in 2008. Complementary medicine also seems to be on the US policy agenda: the recent Senate Committee on Integrative Care: A Pathway to a Healthier Nation received testimony from leaders of integrative medicine (US Senate Committee 2009).

EVIDENCE-BASED COMPLEMENTARY MEDICINE

When faced with the vast array of herbs and natural supplements, the question naturally arises as to which are effective (and in what way and under what conditions), and which are ineffective or potentially dangerous. Attempting to answer this question is extremely complex; it is also compounded by the possibility of either beneficial or harmful interactions with pharmaceutical interventions, and the highly individual physiological, psychological, social and spiritual factors that contribute to overall health status.

Although much empirical wisdom has been handed down through the ages via folklore and systems of traditional medicine, modern medicine attempts to distinguish between different therapeutic options by using the scientific method and the different forms of scientific evidence. In recent times, many herbal and natural supplements have been subjected to thousands of scientific studies in the same way as pharmaceutical medicines have been investigated, and examples of these are found on nearly every page of this book. The scientific study of herbs and natural products adds to previous knowledge and will provide a greater understanding of these medicines.

IN VITRO STUDIES

In vitro testing generally looks at fundamental biological and biochemical processes and can provide important information about biochemical pathways, as well as pharmacokinetic data. Although in vitro tests are helpful, caution should be taken when extrapolating results from them, as the results may not accurately reflect the biological effects seen in the human body.

An example of this is St John's wort. In vitro tests have found that St John's wort inhibits several cytochrome P450 isoenzymes (Budzinski et al 2000, Obach 2000). Clinical tests, however, show that the herb actually has enzyme inducer activity, which is the opposite finding to that of the in vitro tests (Durr et al 2000, Roby et al 2000, Ruschitzka et al 2000).

Anomalies such as this are not restricted to herbal preparations, but have also been observed in regular drug testing. Thus, while

in vitro evidence may be useful, the most accurate method for determining biological activity of a substance is to test it directly in humans (Wienkers 2002).

IN VIVO STUDIES

Studies conducted in animals are able to examine dietary manipulations or administration of experimental agents in specific diseases and deficiency states, and to determine the effects on organ systems and physiological functions. These studies allow for a more rigorous investigation of pharmacological activity than in vitro testing. However, in vivo studies can never be more than suggestive when attempting to assess clinical significance because of interspecies differences. Additionally, the relevance of the dose used must be considered, and extrapolation to clinical relevance in humans is not always accurate.

HUMAN STUDIES

Studies conducted in humans range from anecdotal reports or individual case series, to case–control and cohort studies, and randomised placebo-controlled trials of specific interventions for particular diseases, as well as meta-analyses and systematic reviews of RCTs.

Case reports

Case reports supply informative and realistic information within a clinical setting involving the relevant patient population. Rather than providing definitive information, case reports are merely an investigative starting point for determining clinical relevance.

Extrapolating information from case reports presents some unique challenges and may lead to an overestimation of significance when confounders are not identified and considered carefully. Some of the confounding influences that need to be considered include patient factors such as the placebo effect and concomitant illness and/or the administration or interactions of other agents, as well as factors concerning the substance itself, including errors in labelling, herbal substitution, product adulteration and contamination. It is therefore of prime importance that the product be chemically analysed to confirm its contents, especially when an adverse reaction or interaction is reported in this way.

Randomised controlled trials

Randomised controlled trials (RCTs) provide the most solid foundation for clinical decision making. Those trials performed in the population of patients likely to use the therapeutic agent being tested have the highest validity.

The conduct of an RCT is specifically designed to remove possible sources of bias so that the results are as impartial as possible. The specific nature of RCTs means they cannot answer the general (and non-specific) question as to whether a certain intervention works. An RCT is a specific research tool designed to show whether a specific (active) intervention improves clearly defined outcomes for a specific group of patients suffering from a particular medical condition better than a comparative intervention. These trials are generally defined by four parameters designated by the mnemonic PICO:

- **P** a specifically defined patient **P**opulation
- **I** a well-defined **I**ntervention
- **C** a suitable **C**omparative intervention (often a placebo)
- **O** specific **O**utcome measures.

Although RCTs provide solid evidence, it must be realised that these trials do not always accurately reflect real life, because they are set in a controlled, experimental context with strict inclusion and exclusion criteria and standardised interventions and outcomes. Furthermore, individual variation still occurs, and it is imperative that a study has sufficient statistical power (largely determined by sample size) to be able to detect a clinically relevant result.

Systematic reviews and meta-analyses

When more than one randomised trial has been conducted to answer a particular question, it is possible to statistically combine their results and perform an analysis using the summary statistics from each study as data points. Such a meta-analysis requires that studies use similar measures. By accumulating the results of multiple studies a meta-analysis can provide greater statistical power and therefore a more accurate representation of the relationship under investigation than the individual studies.

Systematic reviews also provide a way of reviewing and summarising the result of multiple RCTs. These reviews attempt to identify all the individual RCTs conducted for an intervention; after systematically examining the methodology and results of each study, they provide a summary of the results and then reach an overall conclusion. Because systematic reviews rely on the results of RCTs, they must be updated regularly as new RCTs are

The Cochrane Collaboration

The Cochrane Collaboration (www.cochrane.org) is an international, not-for-profit collaborative effort that aims to produce up-to-date systematic reviews of all RCTs for both conventional and complementary therapies. The Cochrane Collaboration takes its name from physician and humanitarian Archie Cochrane (1906–88), who strongly advocated the production of critical summaries of research evidence as a way of creating 'evidence-based medicine'.

A systematic review assembles all the RCTs on a given health topic and uses explicit methods to minimise bias (systematic errors) and random error (simple mistakes). It then critically reviews the evidence and summarises the results to determine the safety and effectiveness of an intervention. The Collaboration publishes its systematic reviews quarterly in the Cochrane Library, which is freely available through the National Institute of Clinical Studies via www.nicsl.com.au/cochrane/index.asp.

The Cochrane Consumer Network (www.cochraneconsumer.com) aims to help healthcare consumers make sense of medical research. Its website provides useful information about research jargon and styles, explains how to tell a good study from a bad one, and provides help in finding and understanding health and medical research results.

published. Although many researchers publish systematic reviews, the Cochrane Collaboration has standardised the methodology for performing systematic reviews and regularly publishes results of reviews through the Cochrane Library (see box).

ASSESSING EVIDENCE

There are many dimensions to consider when assessing evidence from clinical studies. Thus, it is important not only to consider the level of evidence, but also to determine the quality of the study (how well the investigators carried out the particular study design), as well as the certainty (statistical precision) of the results. Furthermore, it is important to assess whether the outcome measures and the size of the observed effect are clinically relevant. These dimensions are considered by the NHMRC (2000) and are summarised in Table 1.4.

LIMITATIONS OF EVIDENCE

The rational use of medicines has recently moved towards 'evidence-based care' and recognises that this relies on the conscientious, explicit and judicious use of the *best available evidence* in making decisions about the care of individual patients (Sackett et al 1996). An evidence-based approach recognises both different levels of evidence and that the most rigorous types are not always available. In the light of this, many clinical questions cannot be answered by reference to well-conducted trials and require additional information such as that obtained from experience and historical use.

TABLE 1.4 Dimensions of Evidence

Type of evidence		Definition
Strength of evidence	Level	The study design used, as an indicator of the degree to which bias has been eliminated by design.
	Quality	The methods used by investigators to minimise bias within the study design.
	Statistical precision	The *P*-value or, alternatively, the precision of the estimate of the effect (as indicated by the confidence interval). It reflects the degree of certainty about the existence of a true effect.
Size of effect		The distance of the study estimate from the 'null' value and the inclusion of only clinically important effects in the confidence interval.
Relevance of evidence		The usefulness of the evidence in clinical practice, particularly the appropriateness of the outcome measures.

Source: NHMRC 2000

Randomised controlled trials have been commonly performed only since the 1950s and are complex and costly processes that require large investments of time and money, as well as access to specialised infrastructure and technical and clinical skills. These hurdles are often even higher for herbs and natural supplements than for pharmaceutical medicines, because the lack of patent protection for these products means there is little incentive for companies to invest millions of dollars in research when they cannot obtain a commercial advantage from the results. The relative lack of funding also means that very few research centres are dedicated to exploring this field and few dedicated researchers with the necessary skills are available. Inevitably, there is a smaller scientific evidence base for herbal and natural substances than for synthetic pharmaceuticals.

It is also important to recognise that a lack of evidence for a particular effect does NOT mean that there is evidence for a lack of effect. Put another way, no evidence is not the same as negative evidence. It may simply mean that the research has not yet been conducted because of lack of funding and specialised resources, methodological or logistical constraints and a general lack of opportunity. As a result, there may never be evidence for some treatments, but this does not necessarily mean that the treatment is not effective.

There are several other serious limitations to the sole use of existing scientific evidence, as most are based on statistics that aim to produce results that can be applied to populations of people rather than individuals. Additionally, they are based on averages and probabilities, which also fail to account for individual factors. Thus, despite some recent studies that have attempted to address these issues through novel methodological approaches, the application of scientific evidence is often extremely limited when assessing the effectiveness of individualised therapy.

A further problem arises when trying to make decisions about health rather than disease. Most clinical trials are interested in studying movement across the line that separates 'defined disease' from 'average health' (Fig 1.1). While it is possible to define the particular disease in question through reference to objective parameters, such as biochemical and/or physiological variables, as well as to specific patterns of symptoms, defining optimal health and wellbeing is not as easy. Optimal or enhanced health is a subjective and highly individual state that does not lend itself easily to scientific scrutiny. It is therefore difficult to provide scientific evidence for measures designed to move people from 'average health' towards 'enhanced health' or 'optimal health'.

APPLYING EVIDENCE

Despite the publication of the NHMRC and TGA guidelines for assessing scientific evidence, applying evidence in clinical practice can be extremely complex. Not only does evidence take many different forms, it can also be applied to answer many different types of questions, such as whether a particular therapy works in theory (a question of efficacy) or in clinical practice (a question of effectiveness), as well as whether the use of a therapy is safe and/or cost-effective. Furthermore, there is the question of how a therapy actually works: it is common for evidence to suggest that a therapy is beneficial, even though the mechanism of action remains unknown or, if it is known, for questions about whether the therapy provides clinical benefit to remain unanswered.

The complexity of applying evidence to clinical decision making is compounded by the tens of thousands of studies published every year, with varying degrees of clinical relevance and methodological rigour. Evaluating this evidence can be very confusing, as the results of studies are not always obvious, and their relevance to a particular clinical situation is not always clear. There may also be conflicting results and ongoing controversies in which even the experts disagree. Furthermore, it can be difficult to determine the independence of the information provided, as many influences may be involved: for example, governments, regulatory authorities, commercial interests such as the pharmaceutical, natural medicine and food industries, disease advocacy and consumer groups, the personal interests of the individual researchers and the editorial board, and publication bias.

FINDING EVIDENCE

Obtaining and assessing the available evidence can be both difficult and time-consuming for the busy clinician. Although general medical information is freely available on the internet and via electronic bibliographical databases, fees may need to be paid to access specialised resources for CAM. Additionally, the information available varies considerably in its scope, quality and practicality.

NPS review of complementary medicine information resources

In 2008 the National Prescribing Service (NPS) in Australia commissioned a review of complementary medicine information resources. It aimed to identify high-quality resources that could be recommended for use by Australian health professionals and consumers. A list of 52 information resources from reputable sources was tested against broad criteria encompassing currency, coverage, transparency and content quality to produce a short list of 26 electronic resources. These final resources were evaluated for technical quality, content quality and clinical utility, producing a final list of nine resources.

This book was included in the final list of highest-quality resources, a feat of which the authors are particularly proud, as it was the only resource not to be linked to an online database. A summary of the report can be obtained from the NPS website (www.nps.org.au/research_and_evaluation).

Collections of original research with bibliographical data and abstracts include services such as Medline, Embase, Science Direct and ProQuest. Other databases such as Herbmed, MicroMedex and the Natural Medicines Comprehensive Database provide summaries of current research for numerous herbal and natural medicines. Other collections such as the Cochrane Collaboration Library attempt to produce the most authoritative guide to medical research by providing only systematic reviews of RCTs.

Although databases that provide references to original research are extremely useful, there is a definite need for more summarised and critically reviewed material. This need is met to a certain extent by the publication of review articles in textbooks such as the German Commission E Monographs, or by commercially available databases such as Integrative Medicine Gateway, Natural Medicines Comprehensive Database and the Natural Standard Database.

MISLEADING HEADLINES

Unfortunately, many health professionals do not have ready access to research papers or are too busy to be able to read through full reports and therefore rely on short summaries to provide information. As in the popular press, the medical press is prone to creating sensational headlines to attract interest, but this can lead to inaccurate assumptions. A good example is the case of an apparent coma state brought on by the combination of the herbal medicine kava kava and the benzodiazepine alprazolam. The case was reported with the headline 'Coma from the health food store: interaction between kava and alprazolam' (Almeida & Grimsley 1996). A closer look at the report reveals that the patient described was lethargic and disoriented, but at no time comatose. Additionally, he was also taking cimetidine, a CYP450 inhibitor that can affect alprazolam metabolism, resulting in raised serum levels and symptoms of lethargy. An interaction with kava kava is unlikely.

FACTORS TO CONSIDER IN DECISION MAKING

As previously discussed, scientific evidence provides useful and important information; however, it must be combined with several other important factors in clinical practice to be truly effective for the individual patient. An expanded approach, often discussed as 'evidence-based patient-centred care', is becoming more widely adopted, the chief principles of which are in unison with the integrative medicine approach to incorporating evidence into clinical practice. The key principles may be summarised by the PEACE mnemonic:

- **P** acknowledgment and respect for the **P**ersonal preferences of both the practitioner and the patient
- **E** the strength of the available scientific **E**vidence
- **A** the range of possible **A**lternatives
- **C** the associated **C**osts and risks versus the potential benefits of a proposed treatment
- **E** aspects of **E**xpedience, such as availability, accessibility and immediacy of treatment.

It is easy to become overwhelmed when reviewing the vast range of therapeutic options available, the complexities of accessing and appraising the different types of scientific evidence, and the other factors that must be considered when making choices about treatment options. This evidence-based book is an

attempt to provide some guidance through the current maze of information and evidence. Certainly, more information is needed: in an ideal world every therapy would have clear evidence to support or refute its use in different conditions, and this information would be freely available and without inherent bias. However, that time is still far away, and clinical decision making remains both a subtle art and an inexact science, where there is always room for more information, research and debate.

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CHAPTER 2
INTRODUCTION TO HERBAL MEDICINE

Herbal medicine, also known as phytomedicine, can be broadly defined as both the science and the art of using botanical medicines to prevent and treat illness, and the study and investigation of these medicines. The term 'phytotherapy' is used to describe the therapeutic application of herbal medicines and was first coined by the French physician Henri Leclerc (1870–1955), who published numerous essays on the use of medicinal plants (Weiss 1988).

Phytotherapy can be considered one of the oldest forms of medicine. Since the dawn of time, plants have been used by people of all races, religions and cultures to sustain life and alter the course of disease. Over this time, the medicinal use of plants has evolved along two parallel paths, with the comparatively recent evolution of modern medicine. One path involves the accumulation of empirical knowledge over centuries. Gathered through careful observation of nature and disease, and from cumulative experiences of informed trial and error, the empirical knowledge base for herbal medicines is very large and diverse. For example, the *Rig veda*, a text from India, and the Egyptian papyri *Antiquarium* both date from 3000 BC and contain extensive lists of medicinal plants used to treat illness (Berman et al 1999). In South America, the use of herbal medicine has also been documented, such as in the *Badianus* manuscript, a text written by the Aztecs (Walcott 1940). Their use of herbs, such as datura and passionflower, has been adopted in modern European and American pharmacopoeias. Native Americans were particularly knowledgeable about the botanical medicines in their environment. It has been estimated that more than 200 medicines that were used by one or more Indian nations have been incorporated into the US Pharmacopoeia or National Formulary (Vogel 1970).

Two of the most prominent historical figures in European herbal medicine are Dioscorides and Galen, who were both physicians in ancient Greece. Dioscorides was a Greek army surgeon in the service of the Roman emperor Nero (54–68 AD). He is best known for his *De materia medica*, which describes more than 600 herbs and their uses. Today this work is considered to be the first book ever written about medical botany as an applied science. Galen (131–201 AD) not only wrote several dozen books on pharmacy, but also developed an elaborate system of herbal polypharmacy in which herbal combinations were devised to produce more specific results. The modern term 'galenicals' is still used to describe herbal simples.

Alongside the 'empirical knowledge' approach, a second path developed, which involved a more theoretical and formalised method of diagnosis and treatment. The resulting 'healthcare' systems were complex and often used herbal medicines as an important part of a more comprehensive approach to treatment that also included dietary control, lifestyle changes and spiritual practice. This approach reached its peak in the East with traditional Chinese medicine and Ayurvedic medicine in India.

Although contemporary clinical practice of herbal medicine still relies heavily on traditional wisdom, this knowledge is now being re-examined with the aid of modern analytical methods and scientific methodology. The use of science to establish an evidence base in modern healthcare is changing the way herbalism is being practised and who is using herbs. An

emphasis on phytochemistry and an assessment of risk are inherent features of contemporary research into herbs. While these are important gains in knowledge about the actions and uses of herbs, there is an accompanying shift in the practice of herbal medicine, with less emphasis on the importance of traditional and empirical knowledge, which in time may lead to a loss of the paradigm of holistic and individualised care (Evans 2008). Whether this improves patient outcomes remains to be seen.

HERBS, DRUGS AND PHYTOCHEMICALS

Most pharmaceutical medicines contain a single, highly purified, often artificially produced substance that has a well-known (and occasionally specifically designed) chemical structure that can be patented and owned by the company that developed it. The dosage of these chemicals can also be precisely calculated down to the microgram and can usually be characterised by a very clear pharmacokinetic profile. Additionally, pharmaceutical drugs tend to have a generally agreed upon mechanism of action and series of indications that guide their use within the Western medical model.

As most of these drugs do not exist in nature, they must go through extensive testing to ensure efficacy and safety. New drugs are assessed in test-tube and animal studies for their potential to cause cancer, fetal malformations and other toxic effects, and are ultimately tested on humans to further define the safety profile, pharmacokinetics and drug effectiveness in a targeted disease (Wierenga & Eaton 2003). This process is very costly and requires the application of highly specialised knowledge and infrastructure, as well as many years of concentrated effort. It is estimated that the development of a new drug requires the investment of approximately US$800 million, but it is also extremely lucrative (Di Masi & Grabowski 2003).

PHARMACOGNOSY

In 2001 and 2002, approximately one-quarter of the best-selling drugs worldwide were natural products or derived from natural products. Research on natural products further accounted for approximately 48% of the new chemical entities reported from 1981 to 2002.

Modern drug discovery from medicinal plants has evolved to become a sophisticated process that includes numerous fields of enquiry and various methods of analysis. Typically, the process begins with a botanist, ethnobotanist, ethnopharmacologist or plant ecologist collecting and identifying plants based on the biological activity suggested by their traditional use. Additionally, plants are randomly selected for inclusion in screening programs based on molecular targets identified through the human genome project (Balunas & Kinghorn 2005).

Pharmacognosy is the term used to refer to the study of botanical supplements and herbal remedies, as well as to the search for single-compound drugs from plants. Increasingly, pharmaceutical medicines and preclinical research into herbal medicines are focused on identifying suitable chemical entities that may form the basis for novel treatments (Balunas & Kinghorn 2005).

CHEMICAL COMPLEXITY

In contrast to pharmaceutical drugs, which are based on single molecules that may or may not be derived from natural substances, herbal medicines are chemically complex and may contain many hundreds or even thousands of different 'phytochemicals', including various macro- and micro-nutrients such as fats, carbohydrates and proteins, enzymes, vitamins and minerals. A group of important secondary metabolites are also present, which are generally chemicals used to defend against herbivores, pathogens, insect attack and microbial decomposition, or which are produced in response to injury or infection, or used for signalling and growth regulation. It is these compounds, such as tannins, isoflavones, saponins, flavonoids, glycosides, coumarins, bitters, phyto-oestrogens etc, that are often responsible for the therapeutic properties of herbal medicines (Mills & Bone 2001).

As the secondary metabolites largely dictate a herb's pharmacological nature, a knowledge of herbal chemistry is essential to understand a herb's use and provide valuable insight into its clinical effects. It is sometimes tempting to take the modern reductionist approach and predict the pharmacological activity of a herbal medicine from an understanding of the effects of one key constituent or chemical group; however, this is unlikely to be entirely accurate. In practice, the overall pharmacological activity and safety of each herb is the result of the interaction of numerous constituents, some

of which have demonstrated pharmacological effects, rather than the effect of a single active ingredient.

An example of this is the herb *Paullinia cupana*, commonly known as guarana. As there are limited clinical studies on guarana, it is often reported that the herb owes its pharmacological activity to one key constituent, caffeine, which may be present in concentrations as high as 10%. Studies referring to the isolate caffeine provide some clues about the effects of guarana, but are not entirely accurate, as other important constituents are also present in the remaining 90%. This has been borne out recently in clinical studies of low-caffeine-containing guarana preparations, which still demonstrated significant effects on cognitive function.

Because of the range of phytochemicals present in plants, herbal medicines often include many different active substances with different pharmacokinetics that work at different sites with different mechanisms of action. Herbal medicines therefore potentially have multiple pharmacological actions and many different clinical indications. Furthermore, in addition to the active ingredients, herbs may also contain substances that act to inhibit or promote the active properties, and/or potential unwanted side effects of the active agents. Thus, although specific components may not be active themselves, they may influence the activity of other components by altering their solubility, absorption, distribution or half-life.

For instance, berberine is a constituent of herbs such as goldenseal and barberry and exhibits numerous activities in vitro; however, in vivo, it has poor bioavailability (Pan et al 2002). Berberine has been shown to upregulate the expression and function of the drug transporter P-glycoprotein (P-gp) (Lin et al 1999), thereby reducing the absorption of P-gp substrates. Studies with the P-gp inhibitor cyclosporine have shown that it increases berberine absorption six-fold, as it counteracts the inducing effect of berberine (Pan et al 2002). P-gp inhibitors are also found in nature, such as the virtually ubiquitous quercetin, and when they are present in the same herb competing effects on P-gp expression and function will occur.

The herb St John's wort provides yet another example. The extraction method used in Germany in the product's commercial manufacture was modified in the late 1990s, resulting in higher concentrations of hyperforin than previously obtained (Madabushi et al 2006). Since then, numerous reports and studies have identified pharmacokinetic drug interactions with St John's wort, based on its ability to induce cytochromes and P-gp. It is now well established that hyperforin is the key constituent responsible for these unwanted effects, and St John's wort preparations manufactured with this newer extraction method, such as LI 160, can put people at risk of interactions. Meanwhile, studies with low-hyperforin preparations, such as Ze117, have found that it fails to induce the same interactions (Madabushi et al 2006). Unfortunately, this distinction between St John's wort preparations is not well known and many references and texts fail to mention this important point.

As these examples and many others in this book demonstrate, each herb is chemically complex and produces a pharmacological effect based on the total sum of actions produced by a myriad of constituents that may be acting in synergy. This complexity complicates the ability to test herbal medicines as they are most commonly used (that is, in their more natural states) and in combination with other herbal medicines.

SYNERGISTIC INTERACTIONS

The concept of synergistic interactions is another fundamental difference between herbs and drugs and explains how a single herb may have a number of seemingly unrelated mechanisms of actions and be indicated for a variety of conditions. Intra-herbal interactions between active and apparently non-active constituents also mean that tests performed with single, isolated constituents will not accurately represent the actions and safety of the entire herbal medicine. As such, these tests provide limited information. By and large, it is suspected that it is the intra-herbal interactions that give herbs a broad therapeutic range and very good tolerability.

St John's wort, popularised as a useful treatment for depression, is also an excellent example of intra-herbal interaction. It contains many different constituents, such as hypericin and pseudohypericin, flavonoids such as quercetin and rutin, vitamins C and A, phenolics such as hyperforin, sterols, and an essential oil. Although many of the herb's pharmacological activities appear to be attributable to hypericin and hyperforin, it is now known that the flavonoid content also contributes to its antidepressant activity. In other words, the antidepressant effects identified for isolated

hypericin or hyperforin are greater when the whole herb is used.

In practice, synergistic interactions are used in another important way — herbal polypharmacy. This is the combining of different herbal medicines within the same treatment for a more specific outcome, and is similar to the method Galen described centuries ago. In Chinese medicine the concept of synergistic interactions has reached a great level of sophistication, with Chinese formulas containing as many as 20 different herbs. In that system, the herb possessing the primary action of the formula is considered the 'emperor herb', while 'minister herbs' support the primary action and 'assistant herbs' modify the formula according to the needs of the individual. Finally 'messenger herbs' are used to aid absorption or reduce side effects of the formula. The practice is also common in Ayurvedic medicine and, in fact, in all traditional systems of herbal practice. Although it may be common in conventional medicine to give certain drugs specifically to reduce the side effects of other drugs, such as the administration of antiemetics and laxatives together with opiates, generally the giving of multiple drugs in combination is discouraged. In contrast, in herbal medicine this practice is often considered essential to provide both safety and the best effects.

KEY CONSTITUENT GROUPS

To better understand a herb's mechanisms of action, pharmacokinetics, pharmacodynamics, interactions and side effects, a basic knowledge of the key constituent groups is helpful. Here is a brief outline of the main constituent groups found in popular herbal medicines.

Flavonoids

Flavonoids are plant pigments that are largely responsible for the colour of flowers, fruits and berries. There are many different types of flavonoids including flavones, flavonols, isoflavones and flavins. They are generally anti-inflammatory, antioxidant and anti-allergic, and may decrease capillary fragility. Herbs that are well known for their flavonoid content are ginkgo (*Ginkgo biloba*), St Mary's thistle (*Silybum marianum*) and calendula (*Calendula officinale*).

Flavanols may be further oxidised to yield anthrocyanins. These bluish/purplish compounds contribute to the colour of blueberries and red grapes. They are greatly revered for their antioxidant and anti-inflammatory properties.

Tannins

Tannins are astringent and often taste bitter. They can be divided into two groups, hydrolysable tannins and non-hydrolysable tannins (sometimes called condensed tannins or proanthocyanidins). Tannins have the ability to stabilise proteins and were used historically to tan or preserve animal hides. In herbal medicine, tannins are valued for their ability to dry and tone tissue. Some plants with appreciable levels of tannins include witch hazel (*Hamamelis virginiana*), oak bark (*Quercus robor*) and lady's mantle (*Alchemilla vulgaris*).

Coumarins

Coumarins have a limited distribution in plants and may be either naturally present or synthesised by the plant in response to a bacteria or fungus (Heinrich et al 2004). They are a heterogeneous group, and thus different compounds have various effects on the body. For example, some coumarins demonstrate antispasmodic activity (for example, scopeletin from *Viburnum* spp), others anticoagulant activity (for example dicoumarol from sweet clover), and others anti-oedema effects (for example, coumarins from clivers and red clover).

Alkaloids

Alkaloids are so named for their alkaline properties. This group of phytochemicals has contributed much to modern medicine, and more than 10,000 have been isolated (Evans 2002). Consequently, they are perhaps the best-known constituent group. There are many different types of alkaloids with many different therapeutic properties; however, they commonly contain nitrogen, usually in a heterocyclic ring. Below is a brief outline of the main subgroups:

- **Pyridine, piperidine & pyrrolizidine alkaloids.** Nicotine (*Nicotiana tabacum*) is perhaps the best-known example of the pyridine class. The very poisonous piperidine alkaloid coniine is isolated from hemlock (*Conium maculatum*) and the pyrrolizidine alkaloid senecionine is the reason comfrey (*Symphytum officinale*) was withdrawn from sale in Australia due to concerns over hepatotoxicity.
- **Phenylalkylamine alkaloids.** This group of alkaloids differ in that nitrogen is not part of the heterocyclic ring. The most

commonly known example is ephedrine, a central nervous system stimulant, bronchodilator and vasoconstrictive agent from *Ephedra sinica*.

- **Quinoline alkaloids.** The antimalarial quinine from *Cinchona* spp belongs in this category. Quinine was used in the synthetic production of many antimalarial drugs against *Plasmodium falciparum*. Interestingly, *Plasmodium* has become resistant to the synthesised medications such as chloroquinine, but not to naturally occurring quinine (Heinrich et al 2004).
- **Isoquinoline alkaloids.** Opium, from *Papaver somniferum*, contains over 30 alkaloids, including morphine, codeine, thebaine, papaverine and noscapine. Morphine is well known for its pain-relieving effects. Other examples are the protoberberines, consisting of berberine, berbamine and hydrastine. Golden seal (*Hydrastis canadensis*) contains berberine and hydrastine, barberry (*Berberis vulgaris*) contains berberine and berbamine, and oregon mountain grape (*Mahonia aquifolium*) contains all three. They are strongly antibacterial.
- **Indole alkaloids.** Examples include reserpine from *Rauwolfia serpentina*, which in the past has been used for hypertension; however, its use has largely been discontinued due to toxic side effects. The anticancer agents vincristine and vinblastine, from *Cantharanthus roseus*, are other notable examples.
- **Tropane alkaloids**. Hyoscyamine, from *Atropa belladonna*, is an anticholinergic agent. It has also been used to dilate the pupil of the eye for optical examinations.
- **Xanthine alkaloids.** These are the most widely known and used alkaloids, and include caffeine from tea (*Camellia sinensis*), coffee (*Coffea arabica*) and chocolate (*Theobroma cacao*), which is known to be beneficial to health in small amounts and detrimental in large amounts. Cocoa also contains theobromine and tea contains theophylline and theobromine, both of which are purine alkaloids.

Terpenes

Terpenes are widespread in the plant kingdom. There are many different types:

- **Monoterpene hydrocarbons.** Monoterpenes have a 10-carbon structure. They are major constituents of volatile oils and often have antimicrobial properties. Examples include limonene (lemon, caraway, peppermint and thyme) and alpha-pinene (rosemary, lemon, fennel and eucalyptus).
- **Sesquiterpene hydrocarbons.** Sesquiterpenes have a 15-carbon structure. They are also major constituents of volatile oils and are broadly antimicrobial and insecticidal. Subclasses include alcohols (linalool from lavender, menthol from peppermint), phenols (linalool from lavender), phenols (thymol from thyme, caevacrol from oregano), aldehydes (citronella from citronella), ketones (menthone from peppermint, thujone from wormwood), ethers (anethole from fennel) and esters (methyl salicylate from wintergreen).
- **Diterpene hydrocarbons**. Diterpenes have on average a 20-carbon structure and so are much denser molecules, with higher boiling points, than other hydrocarbons. They are often associated with volatile oils (oleoresins), gums (gum-resins) or with both (oleo-gum-resins) (Evans 2002). Examples include guaiacum resin obtained from *Guaiacum officinale* and gum-resins from frankincense (*Boswellia serrata*).

Glycosides

Glycosides are composed of two parts: the glycone (sugar molecule) and the aglycone (non-sugar molecule). The aglycone may be a terpene, a flavonoid or potentially any other natural compound (Heinrich et al 2004). Below are the most common classes:

- **Triterpene glycosides.** These may also be called saponins. They are a diverse group and exert many different effects on the human body. Depending on their structure, they may be anti-inflammatory (aescin from horse chestnut) or expectorant (senegin from snakeroot), or may demonstrate steroidal effects (glycyrrhetic acid from licorice, diosgenin from wild yam).
- **Glucosinolates.** Also called mustard oil glycosides, these important compounds are found in the Brassicaceae family of vegetables, such as broccoli, mustard and horseradish. They are topically mildly irritant and have digestive, circulatory and anticancer properties when ingested.
- **Cardiac glycosides.** These glycosides have a specific action on heart muscle. They are steroidal in structure and are related to steroidal saponins and phytosterols. A number of herbs contain cardioactive glycosides, including lily of the valley (*Convallaria majus*) and foxglove (*Digitalis* spp). Digoxin

and digitoxin are naturally occurring compounds in digitalis, and digoxin is commonly used in drug form for heart failure.

- **Anthraquinone glycosides.** These compounds have osmotic and stimulant effects in the lower bowel and therefore have laxative properties. Examples of herbs that contain these compounds include cascara (*Rhamnus purshiana*), senna (*Cassia senna*), aloe (*Aloe vera*) and rhubarb root (*Rheum palmatum*).

CHEMOTHERAPEUTICS VERSUS HERBALISM

In practice, drugs and herbs are prescribed quite differently. Drug prescription is often based on the results obtained from clinical trials that measure the effects in populations and use averages to predict outcomes. Investigation and usage is based on the Western medical model and is replicated in almost identical ways by each practitioner who uses this system. By contrast, the same herb may be understood and prescribed in distinctly different ways by different practitioners, depending on the prescribing system being used, with an emphasis on individual prescribing. For example, in Chinese medicine, a herb such as andrographis (*Andrographis paniculata*) is used to clear 'heat' from the blood, because it is considered to be a 'cold' herb, whereas in Western herbalism, it is used to boost immune function and treat the common cold. Further, traditional herbal practice entails combining a number of herbs into a prescription that is tailored to the individual. This customised approach to herbal prescribing is guided by the underpinning paradigm of herbal practice — holism and vitalism. This philosophical basis is lost when herbs are viewed as vehicles for one or two active components or with the increasing cultural emphasis on self-prescribing.

Not only are herbs described and prescribed differently by different medical systems, the properties of herbal medicines are often defined using unique terms not found in drug pharmacology. These properties have traditionally been classified into herbal actions. Thus herbs that relax the gastrointestinal tract and reduce flatulence may be described as carminatives, or those that stimulate bile flow as cholagogues. These actions may be due to particular chemical constituent groups found within the herb or some other property of the herb. Throughout this book, terms specific to herbal medicine and not generally used in drug pharmacology are explained in *Clinical notes*.

Clinical note — German Commission E

The German Commission E is a German government regulatory agency composed of scientists, pharmacists, toxicologists, physicians and herbalists. It has produced a series of monographs based on the available scientific evidence, as well as evidence from traditional use, case studies and the experience of modern herbalists. These monographs are considered to provide authoritative information on herbs, as well as approved indications, contraindications, side effects, interactions, doses, and so on.

In contrast to pharmaceutical medicine, the evidence available to support herbal medicines originally comes from traditional sources, and scientific investigation has only recently been added. Over the past two to three decades there has been an exponential increase in the amount of scientific research being conducted on herbal medicines, chiefly in Europe and Asia, where there are fewer political, economic and regulatory reasons for rejecting traditional medicines. For some herbs there is now sufficient clinical trial evidence to enable meta-analyses to be performed. For many of the popular herbs available over the counter, clinical trial evidence is now being published that can be used to further clarify and determine their place in practice. For others, research may still be in its infancy, with only in vitro testing or testing in experimental models having been conducted so far. Although a general lack of resources, infrastructure, government funding and financial incentive for companies to invest in non-patentable medicines has slowed down investigation, great public popularity continues to fuel further study. Despite the limitations of randomised controlled trials in evaluating complex interventions characterised by traditional herbal practice (Evans 2008), data collections such as the German Commission E monographs are widely cited as gold-standard references, because they use a combination of traditional and scientific evidence to interpret data and make recommendations.

PRODUCT VARIATION AND STANDARDISATION

The chemical complexity of herbal medicines is compounded by the variation that occurs in their production, which starts with the quality

of the original plant material. This may be influenced by the identification methods used (and any misidentification or contamination), genetic variability in the original cultivar and the growing conditions, including the soil type, geographical location, aspect, altitude and climate. Other factors further modify a herb's purity and quality, such as growing techniques (for example, wild harvesting, or organic or conventional farming methods), the timing and method of harvesting, drying, processing and storage, as well as the extraction techniques and solvents used. There are therefore numerous factors that determine the compositional profile of a given herbal extract, and attempts to ensure batch-to-batch consistency are confounded by the inherent chemical complexity of the herb and the natural variations that occur.

As a consequence, clinical research is never simply done on a herb itself. Rather, research must be done on a particular herbal preparation at a specific dose, and the evidence for the efficacy of herbal preparations must be related back to the preparation used in the research. The results of clinical trials are therefore only relevant to the specific herbal preparation that has been tested, at the specific dosage, dose form and route of administration used in the actual trial and cannot necessarily be used to support the use of other extracts or doses of the same herb. The challenge for manufacturers and clinicians, then, is to reproduce a particular preparation, administer it in the proven doses and achieve the expected result. More commonly in practice, herbs are used in variable ways, with different preparations, at a range of doses, and in combination with other herbs or treatments. It is thus hard to guarantee outcomes, either beneficial or adverse, based solely on controlled clinical trials.

STANDARDISATION

Efforts to ensure batch-to-batch reproducibility of herbal medicines have generated a great deal of controversy, particularly involving the term 'standardisation' or the production of so-called standardised extracts. The lack of an agreed definition and the variety of meanings attributed to these terms make them confusing to both consumers and health professionals. Yet they are still used as the basis for product labelling and promotion, where they are used by suppliers for marketing purposes to imply quality, safety or efficacy.

A commonly used (and some may say abused) definition of the term 'standardised' in relation to herbal extracts relies on measuring a specified concentration of an identified constituent or class of constituents known as 'markers'. Markers are usually stable components of a herb that can easily be identified, analysed and measured, but they may or may not be pharmacologically active. An example of this is seen with *Ginkgo biloba*, which is standardised to contain 24% flavonoid glycosides and 6% terpenoids in commercial herbal products, although the active constituents are largely unknown. Sophisticated laboratory techniques are now used to perform this analysis and measurement. Methods include chromatographic techniques, such as thin layer chromatography and high-performance liquid chromatography, both of which provide a visual characterisation of the presence of different chemical constituents, including 'marker' substances in the herb. The graphs produced from chromatographic testing are referred to as 'fingerprints' and are commonly used to determine the identity of herbal material and the integrity of the extraction process, as well as to measure quantities of individual constituents.

Limitations

Although it is generally accepted that herbal standardisation is a useful procedure, it does raise many problems and concerns. First, standardisation to non-active constituents does not necessarily reflect potency. Second, the more perplexing issue of identifying the exact active constituents in a herb is still the subject of much debate for many herbs. Lastly, individual chemical isolates do not fit the accepted definition of a herb, so if the concentration of an isolate is significantly altered for standardisation purposes, the final product may not be truly representative of the original herbal medicine and may even be considered to be 'adulterated' if marker substances are added. Furthermore, despite recent attempts to standardise herbal extracts, there are still no official standards, and herbal products can vary widely with regard to their quality and clinical effectiveness (American Herbal Products Association 2003).

Although conventional pharmaceutical thinking is based on milligrams of an active substance, such an approach is not appropriate for herbal medicines, which have many biologically active, often unmeasurable constituents. Because there can be hundreds of constituents in a complex herbal extract, standardisation is

not possible by merely ensuring that one or two marker constituents are present in the same quantities from batch to batch. The therapeutic actions of herbal medicines rely on the complex combination and interactions of chemicals in the extract rather than on single constituents, and two total extracts can have very different profiles, despite there being a consistent level of one or two marker substances.

The biological activity of any compound, even a marker compound with demonstrated bioactivity, depends on the composition of the rest of the extract. Other components of the extract, even those with no direct physiological effect, may influence the uptake, distribution, metabolism and excretion of other components. Furthermore, this background matrix may affect the solubility, stability and bioavailability of any given compound (Eisner 2001). Thus the presence of chemical markers alone cannot be used to translate clinical evidence from one extract to another.

True standardisation requires more elegant procedures. The American Herbal Products Association has the following definition: 'Standardization refers to the body of information and controls that ensure product consistency from one batch to the next. This is achieved through minimising the inherent variation of natural product composition through quality assurance practices applied to agricultural and manufacturing processes' (American Herbal Products Association 2003). This definition accords more closely with the approach taken in Europe, where process control is an integral component of standardising herbal medicines. The methodology involves proceeding with the aim of standardising all the inputs and processes involved in making a particular extract, in order to ensure batch-to-batch consistency — from the genetic identity of the seed or plant, through to the agricultural processes employed and climatic factors (temperature, rainfall, sunlight), and finishing with drying, processing, extraction, solvent (or solvents), concentration, manufacture, storage, formulation and packaging of the finished product.

In addition to standardising the amount of certain chemical constituents in a herbal preparation, it is also necessary to have a means of standardising doses. Not only can different batches of the same herb have quite different potencies, there are many different formulations. Commercially available herbal preparations include fresh and dried herbs, teas, tinctures, fluid extracts, tablets, capsules and powders, as well as essential oils. When translating doses between different formulations, the amount of dried herb used to produce a set amount of the particular product is often used to give an indication of dosage strength. However, this may not give an accurate indication of potency; for example, fresh grapes, sultanas, grape juice, wine and sherry may all contain the same equivalent dry weight of grapes, but yield very different products with different biological properties.

Because of the lack of formalised standards and the need to prove 'phytoequivalence' for scientific rigour, it is increasingly common for clinical trials to specify the exact dose and extract used and for this information to be used as a basis for government regulation and for marketing purposes. When standardised extracts have been used in clinical trials, this information is included in each monograph.

HERBAL SAFETY

As with all medicines, a risk–benefit profile should be considered before using any herbal medicine. The vast majority of herbal medicines are generally considered to be safe, whether commercially or domestically produced. Most have a wide therapeutic index and only a few have toxic potential. However, adverse reactions may arise from a number of factors and may or may not be predictable. These include inappropriate usage (for example, dose, indication, time frame, administration route) and idiosyncratic reactions such as allergic responses and anaphylaxis.

In addition to adverse reactions arising from the properties of the herb itself, it is also possible for adverse events to arise from contamination or adulteration of herbal products. Contamination occurs when additional substances are inadvertently included in a herbal product. Contaminants can include toxic substances such as heavy metals, pesticide residues and microorganisms, as well as plant material from species other than the intended species, arising from either misidentification or poor quality control. Adulteration, on the other hand, is the intentional inclusion of foreign substances in herbal products, such as pharmaceutical steroids, NSAIDs or synthetic hormones, and may have very serious consequences. The standard of manufacture of commercial herbal products in Australia is generally very high.

Representing Western herbalists in Australia

In Australia, the knowledge and practice of contemporary herbal medicine has been preserved and nurtured mainly by Western herbalists. In fact, the National Herbalists Association of Australia (NHAA) has represented medical herbalists since 1920. Today, many industry insiders consider NHAA to be the industry standard setter for education in medical herbalism. Clinicians are encouraged to check whether herbal practitioners to whom they refer have undergone accredited courses. Further information can be found by contacting the association or accessing the website www.nhaa.org.au.

INTERACTIONS WITH PHARMACEUTICAL DRUGS

One safety issue that has become more recognised over the past decade is the potential for herbs to interact with pharmaceutical drugs. Evidence has emerged to suggest that some herb–drug interactions may be detrimental and have the potential to cause dangerous outcomes, whereas others may be beneficial when an interaction is manipulated to produce positive results (see Chapters 7 and 8).

The popularity of herbal medicine, and the increasing desire among patients for self-treatment and less use of pharmaceutical drugs, have meant that many medical doctors and pharmacists are now dealing with patients who regularly take these types of medicines. As neither doctors nor pharmacists receive comprehensive herbal training as part of their standard education, a potentially detrimental situation can arise in regard to not only patient safety but also negligence. Practical questions, such as whether a herb works in a particular scenario, or is dangerous in another, or compares favourably to a pharmaceutical drug, or can reasonably be expected to have an effect within a certain time frame, are important facts to know. It is hoped that resources such as this text will enable all health practitioners to ensure the safe and rational use of herbal medicines.

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CHAPTER 3
INTRODUCTION TO CLINICAL NUTRITION

Nutrition may be defined as the science of food, its nutrients and substances, and their association with the body in relation to health and disease. In every stage of life, nutrition is important and influences clinical practice in many branches of healthcare. Clinical nutrition is the use of this information in the diagnosis, treatment and prevention of disease that may be caused by deficiency, excess or imbalance of nutrients and in the maintenance of good health.

CONSEQUENCES OF POOR NUTRITION

Nutrition plays a vital role in the health of both individuals and society, with poor nutrition and inadequate intake having a devastating effect. Overall, it has been estimated that more than 60% of all deaths in Australia result from nutrition-related disorders, such as cardiovascular disease, diabetes and cancer (Sydney-Smith 2000).

MORTALITY RISK: CARDIOVASCULAR DISEASE AND CANCER

Atherosclerotic cardiovascular disease is the most common cause of death in most Western countries (Anderson 2003). In Australia, it is the leading cause of death, accounting for 34% of all deaths in 2006. Cardiovascular disease kills one Australian nearly every 10 minutes according to the Australian Heart Foundation website. It is well known that dietary factors such as carbohydrate and fat intake affect several important physiological parameters and risk factors, such as hypertension, lipid levels, diabetes and antioxidant status. With the exception of tobacco consumption, diet is probably the most important factor in the aetiology of human cancers, responsible for around one-third of all cases (Ferguson 2002). Diet-related cancers have often been considered to relate to exogenous carcinogens; however, it is increasingly apparent that many carcinogens may be endogenously generated, and that diet plays an important role in modifying this process (Ferguson 1999).

Overeating and poorly balanced meals have also led to significant increases in metabolic syndrome (syndrome X) and obesity, which are now major health concerns. A 2003 review stated that the World Health Organization estimates there are one billion people around the world who are now overweight or obese, and that 20–25% of the adult population in the USA have metabolic syndrome (Keller & Lemberg 2003).

Although overweight and obesity in adulthood is associated with decreased longevity, and the link with cardiovascular disease is well known, a recent series of meta-analyses revealed statistically significant associations for overweight with the incidence of type II diabetes, all cancers (except oesophageal [female], pancreatic and prostate), asthma, gall-bladder disease, osteoarthritis and chronic back pain (Guh et al 2009). It has further been established that obesity is associated with increased death rates from cancer (Peeters et al 2003). A large prospective study of more than 900,000 people found that a BMI above 40 was associated with a higher combined death rate from all cancers of 52% for obese men and 62% for obese women, compared with people of normal weight (Calle et al 2003). The adverse effects of obesity on health are not limited to adults. Overweight children and adolescents are now being diagnosed with impaired

glucose tolerance and type 2 diabetes, and show early signs of insulin resistance syndrome and cardiovascular risk (Goran et al 2003).

A large body of research exists that attempts to isolate the influence of individual food groups and nutrients on morbidity and mortality. Research with macronutrients has found that the consumption of diets rich in plant-derived foods, wholegrains and fish reduces the risk of morbidity and mortality. However, numerous surveys have identified inadequate intakes of these foods in many Australian subpopulations (Barzi et al 2003, He et al 2002, Mozaffarian et al 2003, Rissanen et al 2003, Slavin 2003). The relative roles of micronutrients, phytochemicals and non-nutrients are still under debate.

FOOD UNDER THE MICROSCOPE

More than 25,000 different bioactive components are thought to occur in the foods consumed by human beings (Milner 2008). These components represent a veritable cocktail of chemicals that includes macronutrients (such as carbohydrates, protein, fat, water and fibre) and micronutrients (such as vitamins and minerals as well as phytochemicals), many of which are health-promoting, plant-based compounds. Additives such as preservatives, colourings and flavourings, together with contaminants introduced through farming or processing techniques, may also be present.

Nutrients can be divided into two main subgroups — essential and non-essential. Essential nutrients are those that cannot be synthesised by the human body in sufficient quantities to meet average requirements, such as vitamin C, and therefore must be taken in through the diet. Non-essential nutrients can be synthesised in the body from other compounds, although they may also be ingested in foods.

MACRONUTRIENTS

Macronutrients supply energy and essential nutrients, making up the bulk of food. Carbohydrates, lipids, proteins, water and some minerals comprise this group and are all necessary to sustain life. Some macronutrients are produced in supplement form and are used as therapeutic agents. As a result, a number of these are reviewed in this book.

Carbohydrates

Simple carbohydrates, also known as sugars, are termed 'monosaccharides' because they are the single sugar units that form the basis of all sugar structures. Glucose is a monosaccharide and the primary source of energy for most human cells. Most glucose is not ingested through the diet, but rather synthesised from sucrose (common sugar) in the liver (Wardlaw 1997). More complex forms of carbohydrates, such as starches and fibres, are composed of many units of smaller carbohydrates found in grains, vegetables and fruit and are termed 'polysaccharides'. Overall, carbohydrates are important as a fuel. They are considered protein-sparing, as they prevent the breakdown of proteins in the muscles, heart and liver into amino acids and ultimately glucose to produce fuel.

Lipids

The term 'lipid' is a generic one used to describe a number of chemicals that share two main characteristics: they are insoluble in water and contain fatty acids. When they are solid at room temperature, they are called fats, whereas those that are liquids are called oils. Fatty acids are the simplest form of lipids, and more than 40 different types occur in nature (Wahlqvist et al 1997). Of all the various classes of lipids, only precursors of the omega-3 and omega-6 fatty acids are considered essential, meaning they are necessary in the diet to maintain health. The amount of dietary fat ingested and the ratios between saturated, monounsaturated and polyunsaturated fatty acids are important influences on overall health and disease.

Protein

Protein is formed by linking individual amino acids together, with the order of the amino acid sequence determining the protein's ultimate form and function. Proteins are crucial to the regulation and maintenance of many vital body processes, such as blood clotting and fluid balance, cell repair, and hormone and enzyme production.

Amino acids can be divided into two broad groups: essential or non-essential. There are nine essential amino acids that must be ingested through the diet to maintain health. Protein foods that contain all nine essential amino acids are also referred to as complete protein sources (e.g. animal protein). By contrast, almost all plant foods are incomplete protein sources, with the possible exception of spirulina and soy. During times of growth, tissue repair or pronounced catabolism, such as after surgery, the body requires additional protein

for efficient new tissue growth to occur. There is also emerging evidence that supplementation with individual amino acids produces a variety of pharmacological effects that can be manipulated to provide therapeutic benefits. Several of these amino acids are reviewed in the monograph section.

Minerals

Some minerals fall into the category of macronutrients because they are required in gram amounts every day, although they do not directly produce energy. These include sodium, potassium, calcium, phosphorus and magnesium.

MICRONUTRIENTS

Micronutrients do not in themselves provide energy or fuel for the body, but they may be involved in the chemical processes required to produce energy from macronutrients.

Vitamins and trace minerals fall into this category and are required to sustain life, typically through their roles as enzymatic co-factors in diverse biochemical processes. Many micronutrients are available in supplement preparations and are reviewed in this book.

Vitamins

Vitamins are organic substances (i.e. they contain a carbon atom) essential for normal growth and functioning of the body. They have been divided into two broad groups: vitamin C and the eight members of the B complex (B_1, B_2, B_3, B_5, B_6, B_{12}, biotin and folic acid) are defined as water-soluble vitamins, whereas vitamins A, D, E and K are fat-soluble. Levels in the body need to be replenished on a regular basis, as only vitamins A, E and B_{12} are stored to any significant extent. Just as a vitamin deficiency causes adverse outcomes, high doses of these supplements can also do so if used inappropriately.

Essential trace minerals

These are minerals required by the body, usually in milligram or microgram amounts. They include iron, iodine, fluoride, zinc, chromium, selenium, manganese, molybdenum and copper. All trace minerals have the potential to be toxic when consumed in high doses.

Phytochemicals

Phytochemicals are components in plant foods that appear to provide significant health benefits, yet are not essential. Considerable research

TABLE 3.1 The Chemical Complexity of Food

Nutrients	
Micronutrients	Vitamins: A, B complex, C, D, E, K, coenzyme Q10 Minerals: iron, iodine, fluoride, zinc, chromium, selenium, manganese, molybdenum and copper Others?
Macronutrients	Carbohydrates: simple and complex Proteins: amino acids Lipids: saturated, monounsaturated and polyunsaturated fatty acids Fibre: soluble and insoluble Water Minerals: sodium, potassium, calcium, magnesium, phosphorus Others?
Phytochemicals	Bioflavonoids, carotenoids, isoflavones, glutathione, lipoic acid, caffeic acid, ferulic acid, lignans, allyl sulfides, indoles
Non-nutrients	
Food additives: natural or synthetic	Colourings: restore colours lost during processing or alter natural colour Flavourings: alter natural flavours Preservatives: prolong shelf-life by reducing bacterial, mould and yeast growth Thickeners: modify texture and consistency of food Humectants: control moisture levels and keep food moist (mainly used in baked foods) Food acids: used to standardise acid levels between different food batches Antioxidants: used to preserve foods mainly containing fats and oils
Contaminants	Natural contaminants Industrial pollutants Processing contaminants Others?

Source: Wahlqvist et al 1997, Wardlaw 1997

has been undertaken in the past few decades to understand the role they play in maintaining health and preventing certain diseases, such as cancer, but there is still much to learn. Some of the better known phytochemicals include isoflavones (e.g. genistein), bioflavonoids (e.g. procyanidins), carotenoids (e.g. lycopene), glutathione and alpha-lipoic acid. Many of the phytochemicals found in food are also found in medicinal herbs and may partly explain their therapeutic qualities.

FOOD LABELS

According to Nutrition Australia, by law all packaged foods must carry labels that state the following information:

- name of food
- name and business address of manufacturer
- country of origin
- ingredients, listed by weight from greatest to smallest (including added water)
- percentage of the key ingredient or component present in the food product
- warnings about the presence of major allergens in the food, such as nuts, seafood, eggs, gluten and soy
- a nutrition information panel, unless the food is not packaged or the package is too small (e.g. tea bags)
- an expiry date.

For further information about labelling, see Food Standards Australia New Zealand website at http://www.foodstandards.gov.au/thecode/.

Currently, more than 35 genetically modified (GM) foods have been approved for sale in Australia and New Zealand (FSANZ 2009), including foods derived from soy, sugar beet, corn, cottonseed oil, canola and potatoes. As from December 2001, labels must also state whether a food contains a GM-derived component or protein introduced through genetic modification.

Additives are listed as either numbers, known as additive codes, or by name. Up-to-date lists of the food additives found in Australian and New Zealand food products can be located at <www.foodstandards.gov.au>.

NUTRITIONAL DEFICIENCIES

Malnutrition and other deficiency states, such as kwashiorkor (protein deficiency), scurvy or rickets, are major causes of morbidity and mortality in both developing and developed countries under conditions of deprivation. Malnutrition can occur as a result of alcoholism, medication use, fussy eating, anorexia, small bowel obstruction and numerous other medical conditions.

More specific or individual nutritional deficiencies can be classified as either a 'primary deficiency' or a 'secondary deficiency', according to their aetiology.

PRIMARY DEFICIENCY

Primary deficiency is defined as a state arising from inadequate dietary intake. Although considered to be rare in developed countries, inadequate intake and primary deficiency states are not uncommon, as evidenced by numerous dietary surveys both here and overseas.

Inadequate dietary intake

The Australian National Nutrition Survey (NNS) conducted in 1995 found that approximately 30% of 2–7-year-old children ate no fruit or vegetables. Among 8–11-year-olds, 44% of boys and 38% of girls ate no fruit on the previous day and approximately one in four older children consumed no vegetables. Additionally, neither age group consumed the minimum number of serves of dairy products (Cashel 2000). Later results from the Australian Institute of Health and Welfare in 1998 reported that approximately one in two Australian children under 12 were not eating fruit or fruit products, and more than one in five consumed no vegetables in a typical day.

The dietary intakes of adults are also far from ideal. The 1995 NNS also found that approximately 44% of adult males and 34% of females did not consume fruit in the 24 hours preceding the survey, and 20% of males and 17% of females did not consume vegetables (Giskes et al 2002).

Interestingly, dietary intakes were influenced by income level, with lower-income adults consuming a smaller variety of fruits and vegetables than their higher-income counterparts. Additional research has consistently identified other groups at risk of poor dietary habits, such as the elderly, institutionalised individuals and the indigenous population.

Surveys of individual vitamin and mineral intakes also identify a number of at-risk subpopulations. Calcium intakes for 1045 randomly selected Australian women (20–92 years) as estimated by questionnaire showed that 76% of women aged 20–54 years, 87% of older women and 82% of lactating women had intakes below the recommended dietary intake

(Pasco et al 2000). Of these, 14% had less than the minimum requirement of 300 mg/day and would, therefore, be in negative calcium balance and at risk of bone loss. The 1997 New Zealand National Nutrition Survey found that 20% of all New Zealanders and one in four women had calcium intakes below the UK estimated average requirements, and 15–20% of women aged 15–18 years were considered to have frank deficiency (Horwath et al 2001).

Surveys in Australia and New Zealand report that many adolescent girls have insufficient dietary intakes of iron and zinc to meet their high physiological requirements for growing body tissues, expanding red cell mass, and onset of menarche (Gibson et al 2002).

Evidence of deficiency in Australia and New Zealand

It is a common perception that although dietary intakes are not ideal, vitamin and mineral deficiencies are not a major health concern; however, research has shown that several subpopulations, such as children, pregnant and lactating women, older adults, institutionalised individuals, indigenous peoples and vegetarians, are at real risk.

For example, several local surveys have found that mild to moderate iodine deficiency is more prevalent than once thought (Li et al 2001). This is of great concern because mild iodine deficiency during childhood and pregnancy has the potential to impair neurological development. One survey of Sydney schoolchildren, healthy adult volunteers, pregnant women and patients with diabetes found that all four groups had urinary iodine excretion values below those set by the World Health Organization for iodine repletion (Li et al 2001). Another survey of 225 children in Tasmania identified evidence of mild iodine deficiency in 25% of boys and 21% of girls (Guttikonda et al 2002). A research group at Monash Medical Centre in Melbourne screened 802 pregnant women and found that 48.4% of Caucasian women had urinary iodine concentrations below 50 micrograms/L compared to 38.4% of Vietnamese women and 40.8% of Indian/Sri Lankan women (Hamrosi et al 2005). These figures are disturbing when one considers that normal levels are over 100 micrograms/L, mild deficiency is diagnosed at 51–100 micrograms/L and moderate to severe deficiency at < 50 micrograms/L (Gunton et al 1999). A study conducted at a Sydney hospital involving 81 women attending a 'high risk' clinic found moderate to severe iodine deficiency in 19.8% of volunteers and mild iodine deficiency in another 29.6% (Gunton et al 1999).

In Australia and New Zealand, the prevalence of vitamin D deficiency varies, but it is now acknowledged to be much higher than previously thought (Nowson & Margerison 2002). The groups at greatest risk are dark-skinned and veiled women (particularly in pregnancy), their infants, and older persons living in residential care. The study by Nowson and Margerison found marginal deficiency in 23% of women, and another frank deficiency in 80% of dark-skinned women in Australia. A study conducted in a large aged-care facility in Auckland identified frank vitamin D deficiency in 49% of elderly participants in midwinter and in 33% in midsummer (Ley et al 1999). Even in studies of 'healthy' adults, vitamin D insufficiency has been found to affect more than 40% of residents in Queensland (Kimlin et al 2007, van der Mei et al 2007) and over 65% of Tasmanians (van der Mei et al 2007).

Barriers to good nutrition

Clearly, living in a developed country is not a guarantee of healthy nutrition. Western first-world countries have a wide range of good-quality foods available at affordable prices, yet healthy eating is not commonplace. There are four key levels of influence on dietary behaviours:

1. individual factors
2. interpersonal factors
3. organisational factors
4. environmental factors.

At each level, barriers to healthy eating behaviours exist. Table 3.2 (p 28) lists some of the more common barriers. Successful nutritional interventions that aim to modify individuals' eating patterns should help people develop new routines and simple internalised rules that they can use to navigate sensibly through the multitude of food choices and personal influences.

Nutritional intervention is a central component of disease prevention and management. Health professionals play a pivotal role in undertaking nutritional interventions with patients because of their knowledge, access to information and credibility as patient educators.

SECONDARY DEFICIENCY

Secondary deficiency may develop when there is reduced nutrient absorption, or increased metabolism or excretion of any given nutrient.

TABLE 3.2 Influences over Food Choices	
Nutritional knowledge	Income: food choices based on affordability
Religious beliefs and practices	Childhood experiences
Family beliefs and practices	Dental health: for example, ill-fitting dentures, sensitive teeth
Cultural beliefs and practices	Availability and convenience: for example, convenience of fast food
Ethnicity	Muscle weakness or joint pain: problems with shopping and cooking
Education	Problems chewing and swallowing
Occupation	Gastrointestinal problems: for example, nausea, diarrhoea
Peer and social influences	Following a specific diet: for example, fad diets
Advertising	Psychosocial problems: loneliness, depression, confusion, isolation
Emotional factors: for example, indulging in 'comfort' foods	
Medication: dietary alterations may be necessary; side effects may alter appetite	
Food: flavour, texture, appearance, odour	

Of these, malabsorption states are the most common and associated with many diseases such as those characterised by chronic diarrhoea (e.g. Crohn's disease), alterations to gastrointestinal tract architecture (e.g. coeliac disease) and liver cirrhosis. In these cases, malabsorption may be specific to certain nutrients and fats or may be more generalised.

The effects of pharmaceutical medicines on nutritional status must not be forgotten. A significant number of drugs affect appetite, nutrient absorption and synthesis, transport and storage, metabolism and excretion. In fact, some of the side effects of medicines may not be related to the medicine directly, but rather to the nutritional deficiencies that develop with their use over time. These will not always produce clinically significant adverse effects, but when combined with a poor diet, or when several medicines affecting the same nutrients are taken, the risk of deficiency is heightened.

Medicines that can reduce intake of nutrients include those that induce nausea, dyspepsia, or decrease appetite, such as non-steroidal anti-inflammatory drugs (NSAIDs), and opioid drugs such as codeine and morphine. Medicines with the potential to reduce nutrient absorption include those that reduce gastric motility (e.g. opioid drugs), greatly increase gastric motility (e.g. metoclopramide), compromise digestive enzyme output and function (e.g. proton pump inhibitors), and bind nutrients, preventing their traverse across gastrointestinal membranes, such as anion exchange resins (e.g. cholestyramine). Certain medicines can also increase nutrient excretion, such as thiazide diuretics, which increase potassium excretion. Others can reduce vitamin biosynthesis, such as statins, which reduce the production of coenzyme Q10.

In each of these cases, either increased nutritional intakes may be required to offset possible depletions, or medicines should not be administered with meals or supplements to reduce the likelihood of more direct interactions.

RDA AND RDI REFERENCE VALUES FOR AUSTRALIA AND NEW ZEALAND

The concept of recommended daily allowances (RDAs) originated in the United States in the 1940s as a basis for setting the poverty threshold and food-stamp allocations for the military and civilian populations during times of war and/or economic depression (Russell 2007). At this time, the first RDAs were determined by observing a healthy population's usual dietary intakes and extrapolating RDAs from this information. Over the subsequent decades, scientific research into health and nutrition became more sophisticated, rendering the original concept of RDAs incomplete and in need of modification. The main findings to emerge were as follows:

1. Many additional nutrients found in food are important for health, so a longer list of nutrients with recommended levels will be required.
2. Nutrient intake recommendations need to be related to a specific use, as requirements will vary for different subpopulations.
3. Nutritional intake recommendations need to take into account longer-term disease prevention, not just deficiency prevention.
4. Clearer endpoints will be required by which to set adequacy levels.

5. Risk assessment of nutrients will be necessary.

In the mid-1990s a new framework was developed to address these issues. It aimed to establish new nutrient intake recommendations to meet a variety of uses and to base nutrient requirements on the reduction of chronic disease risk, with a clear rationale for the endpoints chosen. The new guidelines still contain RDAs, but have been expanded to include three new intake recommendations: estimated average requirements (EARs), adequate daily intake (ADI) and upper level (UL) of intake.

Revisions to the nutrient intake framework occurred all around the world and in 2006 the National Health and Medical Research Council (NHMRC) of Australia published its adjusted nutritional guidelines for the adequate intake of vitamins and minerals (NHMRC 2006). These guidelines were far more comprehensive than previous versions and incorporated some of the initiatives developed in the United States.

The NHMRC guidelines are intended for healthy people and specify requirements based on both gender and age, while assuming average body weights of 76 kg for the adult male and 61 kg for the adult female.

Four key dietary reference value terms are defined here:

1. **Estimated average requirement (EAR).** A daily nutrient level estimated to meet the needs of 50% of the healthy population in a particular life cycle and gender.
2. **Recommended daily intake (RDI).** A daily nutrient intake estimated to meet the needs of up to 98% of healthy people in a particular life cycle and gender. This remains the most common benchmark of individual nutrient adequacy.
3. **Adequate daily intake (ADI).** When RDI cannot be determined, this is based on observed or experimentally derived estimates of daily nutrient intake to meet the needs of healthy individuals.
4. **Upper level (UL) of intake.** An estimate of the highest level of regular intake that carries no appreciable risk of adverse health effects to almost all people in the general population. It is meant to apply to all groups of the general population, including sensitive individuals, throughout the life stages.

In some instances, the 2006 RDI values for specific nutrients represented a substantial increase (e.g. iron and folate), whereas others increased only marginally (e.g. calcium) or decreased (e.g. zinc requirements for adult females).

RDI and nutritional deficiencies

Although the RDIs provide a guide to preventing nutrient deficiency signs and symptoms in a 'healthy' population, they are only general recommendations and do not take into account each individual's requirements or specific circumstances. As a result, seemingly adequate food intake can provide false security, owing to a number of factors that influence the nutritional content of food and the way important nutrients are absorbed, utilised and excreted.

Unfavourable cooking and storage conditions can significantly reduce the nutritional content of food before it is consumed, no longer providing the expected vitamins and minerals. Many vitamins and minerals are sensitive to changes in temperature, light and oxygen. Up to 50% of vitamins A, D and E and 100% of vitamin C and folate can be lost during cooking (Wahlqvist et al 1997).

Issues relating to various farming techniques have often been cited as affecting the nutritional content of food and are readily reflected in the variability of resulting mineral composition. A good illustration of this is selenium, which, like most other minerals, enters the food chain through incorporation into plants from the soil. Plants grown in soils with low selenium levels are likely to contain smaller quantities than those grown in selenium-rich soils. Acid soils and complexation with metals, such as iron or aluminium, also reduce plant selenium content.

Beyond the actual quantities of nutrients provided by our food, reduced bioavailability of nutrients can occur as a result of interactions between food constituents. Phytates found in dietary fibre and tannins found in tea (and several herbal medicines) are able to bind to iron, zinc and other minerals, impairing the body's ability to absorb them. Therefore, adequate intake of mineral-rich food does not necessarily prevent deficiency. In addition to this, there are other potential contributors to secondary nutrient deficiencies, such as impaired absorption, compromised or accelerated utilisation, and increased excretion of individual nutrients as well as genetic variables.

Serious deficiencies of reference values

Setting nutrient reference values is a complex task, which produces only approximate values. Russell from the Human Nutrition Research Centre on Aging at Tufts University has outlined eight different obstacles that prevent

accurate determination of reference values (Russell 2007):

1. Few long-term studies are available so information is extrapolated from short-term studies (e.g. 1–2 weeks).
2. Little good quality information is available about individual variability in response to the indicators in question.
3. Most research fails to consider the interaction between nutrients (which may be important for good health).
4. Many databases used when determining reference values provided information from studies that evaluated only dietary intakes and ignored supplemental intakes.
5. Most studies fail to consider the variation in nutrient bioavailability that is influenced by the food matrixes in which the nutrient presents.
6. Little good quality information is available about children, adolescents and the elderly from which to establish reference values with any degree of certainty.
7. Little good quality dose-response information is available (i.e. responses to multiple levels of the same nutrient in the same individual).
8. The cause and effect of a nutrient on a specific outcome is sometimes still speculative, as multiple factors may affect an outcome, not simply a single nutrient.

The obstacles outlined here clearly indicate that *the scientific basis for many of the reference values is weak*. They also indicate that for many nutrients and food components the RDI and UL levels are only approximations that are loosely relevant to the general healthy population, and even less relevant to the individual with comorbidities or special needs. Substantial research would be required to create a set of reference values with greater accuracy and relevance, but even then some values, such as ULs, may never be entirely accurate, as ethical considerations would prevent such research from ever being conducted.

OPTIMAL NUTRITION: A STATE BEYOND RDI

Dietary reference values are based on the concept of nutrient requirement. When considering these, it is important to keep in mind how we define or identify 'adequacy'. Historically, one measure of adequacy has been the dose of nutrient required to prevent the clinical manifestations of the corresponding deficiency. This method has yielded RDI reference values, which prevent overt deficiency presentations in most healthy people but do not guarantee the prevention of a less well defined suboptimal intake that may over time contribute to other pathology.

There is considerable evidence some nutrients may have health benefits at intake levels greater than the RDI. Higher intake levels appear to play a role in the prevention of many degenerative diseases such as cancer, cardiovascular disease, macular degeneration and cataract, cognitive decline and Alzheimer's dementia, as well as of developmental conditions such as neural tube defect. The NHMRC guidelines for the adequate intake of vitamins and minerals acknowledge this fact and state that 'there is some evidence that a range of nutrients could have benefits in chronic disease aetiology at levels above the RDI or AI' (NHMRC 2006).This has given rise to a new concept, 'suboptimal nutrition'.

The phrase 'suboptimal nutrition' was first coined by Fairfield and Fletcher in their 2002 systematic review evaluating the evidence indicating that certain nutrients had long-term disease prevention properties (Fairfield & Fletcher 2002). They defined suboptimal nutrition as a state in which nutritional intake is sufficient to prevent the classical symptoms and signs of deficiency, yet insufficient to significantly reduce the risk of developmental or degenerative diseases. As such, avoiding a state of suboptimal nutrition requires adequate dietary intakes of all key food groups with an emphasis on health-promoting foods, and possibly the use of additional nutritional supplements. Furthermore, the balance between micronutrients or macronutrients is important, such as the ratio of omega-3 to omega-6 fatty acids and of high to low glycaemic carbohydrates.

Huang et al extended this work and conducted another comprehensive review to determine whether evidence supported the use of multivitamin/mineral supplements and certain single nutrient supplements in the primary prevention of chronic disease in the general adult population (Huang et al 2006). This review concluded that multivitamin/mineral supplement use may prevent cancer in individuals with poor or suboptimal nutritional status.

As a reflection of these new developments, the term 'suggested dietary target' has been adopted by the NHMRC to describe the 'daily average intake from food and beverages for certain nutrients that may help in prevention

of chronic disease'. It is a move that recognises that food components offer more than just deficiency prevention; however, the general recommendations still relate only to the general healthy population.

Theoretically, it can be imagined that there is a level of intake that could be considered to provide optimal nutrition that is above the RDI yet below the UL levels. Figure 3.1 illustrates a theoretical description of beneficial health effects of a nutrient as a function of level of intake. The solid line in the figure represents risk of inadequacy in preventing nutritional deficiency and the broken line represents the risk of inadequacy in achieving a health benefit, that is, disease risk reduction (Renwick et al 2004). As intake falls below the RDI, the risk of adverse effects due to inadequate intake increases, and as intake increases beyond an optimal level, there is an increased risk of adverse effects due to toxicity. Naturally, however, such an optimal intake may be highly individualistic, based on the previous discussion of confounding factors.

Redefining an essential nutrient

Clearly the line between essential and non-essential nutrients has blurred as a result of modern scientific inquiry and experimentation (Yates 2005). In the first half of the 20th century, nutrients were termed 'essential' when their removal from the diet caused severe organ dysfunction or death. Since then, modern scientific techniques have enabled us to detect finer gradations of inadequacy well before organic pathology, such as a decline in health status or ability to function optimally, sets in. They have also allowed us to glimpse the potential of nutrients and certain food compounds to prevent genomic mutations, alter metabolic processes and ultimately prevent disease, possibly even extending longevity concomitantly. If we broaden the aim of nutrition beyond prevention of deficiency to include the promotion of wellness and optimal health, many additional nutrients and food components are likely also to be able to be termed 'essential'.

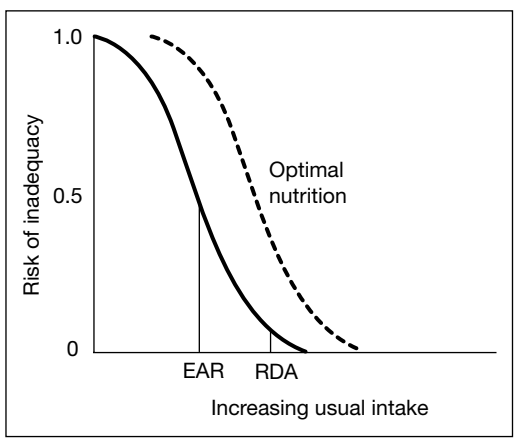

FIGURE 3.1 A theoretical description of beneficial health effects of a nutrient as a function of level of intake (Renwick et al 2004)

NUTRITIONAL GENOMICS

Nutritional genomics is a field that has emerged alongside the Human Genome Project. It has a unique focus on disease prevention and healthy ageing through the manipulation of gene–diet interactions. Several key scientific domains in nutritional genomics focus on specific areas of this interaction.

Nutrigenomics, also known as nutritional epigenetics, refers to the effect of nutrients on gene expression. Involving the identification, classification and characterisation of human genetic variants or polymorphisms (mutations) that modify individual responses to nutrients (Fig 3.2), its application in the manipulation of biological pathways to produce health benefits is called systems biology, or nutritional engineering. This opens up the possibility of truly individualised nutritional management through its potential to compensate for

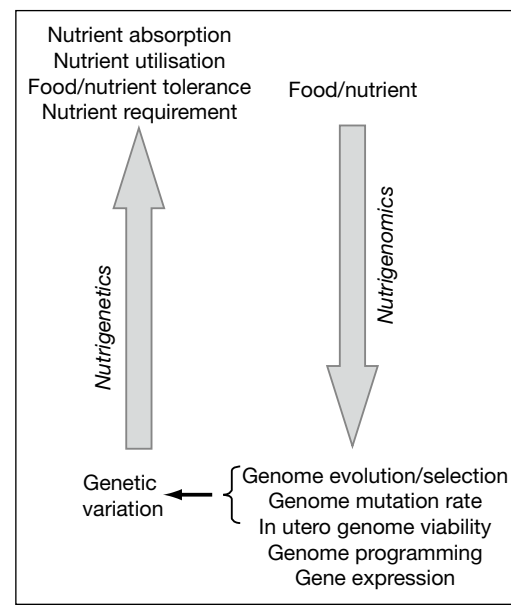

FIGURE 3.2 Nutrient genome interactions (From Stover and Caudill 2008)

EURRECA: Europe's new collaboration

EURRECA stands for EURopean Micronutrient RECommendations Aligned. Its overall objective is to create a sustainable collaborative network to develop science-based aligned nutrient recommendations across Europe with special focus on vulnerable groups and consumer understanding (Pijls et al 2009).

To better understand inter-individual variation and its determinants, EURRECA plans to establish the quantitative extents to which genetic, epigenetic and dietary factors determine the nutritional phenotype, as well as the way in which they interact in doing so.

For more details about EURRECA, see <http://www.eurreca.org>.

metabolic deficiencies and genetic susceptibility, simply by using dietary modification and nutritional supplementation (Stover & Caudill 2008).

It is widely considered that nutritional genomics holds the promise to revolutionise both clinical and public-health nutrition practice in other ways. These include facilitating the establishment of genome-informed nutrient and food-based dietary guidelines for disease prevention and healthy ageing, and better targeted public health nutrition interventions (including micronutrient fortification and supplementation) that maximise benefit and minimise adverse outcomes in genetically diverse human populations (Stover & Caudill 2008).

Nutritional genomics will also revolutionise the conduct and interpretation of clinical trials and epidemiological studies that investigate the associations between diet and/or nutritional supplementation and disease. This knowledge can be used to distinguish between responders and non-responders, and to determine which populations are most likely to benefit from nutritional intervention and which may be at increased risk of harm.

NUTRITIONAL DEFICIENCY, GENOME DAMAGE AND CLINICAL PRACTICE

There is overwhelming evidence that several micronutrients (vitamins and minerals) are required as co-factors for enzymes or as part of the structure of proteins (metalloenzymes) involved in DNA synthesis and repair, prevention of oxidative damage to DNA as well as maintenance methylation of DNA. The main point is that genome damage caused by moderate micronutrient deficiency is of the same order of magnitude as the genome damage levels caused by exposure to significant doses of environmental genotoxins such as chemical carcinogens, ultraviolet radiation and ionising radiation (Fenech 2008). For example, deficiency of vitamins B_{12}, folic acid, B_6, C, E, or iron or zinc appears to damage DNA in the same way as radiation, by causing single- and double-strand breaks, oxidative lesions or both. Half of the population may be deficient in at least one of these micronutrients (Ames 2004). If moderate deficiency in just one micronutrient can cause significant DNA damage, it is possible that multiple moderate deficiencies may have additive or synergistic effects on genome stability.

Current research indicates that the amount of micronutrients that appear to be protective against genome damage varies greatly between foods, and careful choice is needed to design dietary patterns optimised for genome health maintenance. Because dietary choices vary between individuals, several interventional options are required, and nutritional supplements may be necessary to fill in gaps not met by food intake, or to elevate intake levels beyond dietary intake to influence key metabolic pathways.

As the field of nutritional genomics matures, healthcare practitioners will have the opportunity to make genetically individualised dietary recommendations aimed at improving human health and preventing disease (Milner 2008). It is possible to envisage preventative medicine being practised in 'genome health clinics', where clinicians would diagnose and nutritionally prevent the most fundamental initiating cause of developmental and degenerative disease — genome damage itself (Fenech 2008).

NUTRITIONAL SUPPLEMENTATION

Nutritional supplements have traditionally been recommended only in cases of established deficiency; however, scientific evidence is accumulating to suggest they may be an important extension of healthy eating and necessary to achieve a level of health and disease prevention beyond what is possible through diet alone. As a consequence, many conservative medical bodies are being forced to re-assess their long-established views.

Clinical note — Taking a multivitamin may save billions of dollars

In October 2003, the first ever report to quantify the preventative health benefits of multivitamin supplementation using the US health insurance model was released (DaVanzo et al 2003). After an extensive review of the scientific literature combined with an analysis of Medicare claims and Congressional Budget Office accounting methods, it was established that multivitamin use by older adults could lead to Medicare cost savings of more than US$1.6 billion over the next 5 years. Significant cost savings were based on improved immune function and a reduction in relative risk of coronary artery disease achievable with daily multivitamin supplementation in people over 65 years old. The Lewin Report states that these findings are conservative, as they do not take into account cost savings from decreased ambulatory care and the assumption was that only one-third of adults will experience benefits. Additionally, reductions in the incidence of other diseases were not considered. In conclusion, researchers found that a daily multivitamin supplement is a safe, relatively inexpensive and yet potentially powerful way of improving one's health.

In Australia and New Zealand, the situation is different. Local medical journals include information about nutritional research from time to time, but there is still a sense that a balanced diet will be adequate for most healthy people.

In 2002, a review in the *Journal of the American Medical Association* of both the clinical and the scientific literature on vitamins and their relationship to health and disease came to a conclusion vastly different from medical profession's traditional view (Fairfield & Fletcher 2002). This comprehensive review of 30 years of scientific research supported the concept of suboptimal nutrition, finding it was relatively common and associated with many major chronic diseases. As a result, it was recommended that clinicians counsel patients to improve their diets, and that all adults should take a daily multivitamin (Fletcher & Fairfield 2002).

Evidence supporting the use of multivitamin/mineral supplements as nutritional insurance has continued to accumulate. The consistent finding is that such an intervention would markedly improve health — for example, in cases of heart disease, cancer, immune function and cataracts, particularly for the poor, the young, the obese and the elderly (Ames 2004). The caveat is, of course, that too much of a supplement may be toxic.

SAFETY ISSUES

Nutritional supplements can be viewed as medicines that have both subtherapeutic and toxic doses, as well as the potential to induce adverse reactions and interactions.

Adverse reactions and interactions

The same subpopulations that have been identified to be at greater risk of adverse reactions to pharmaceutical medicines may be used for the safety assessment of nutritional supplements. These groups are the elderly, atopic patients, people with compromised liver or kidney function, anxiety or depression, or serious illness, and those already taking many medicines. In clinical practice, the risk-versus-benefit decision of recommending a supplement or not is always considered and should be discussed with patients. In many cases, the risk of experiencing a minor adverse reaction that is short-lived and not serious may be an acceptable risk, whereas the risk of a more serious adverse reaction is not.

Toxicity

If a toxic dose is defined as one that is capable of causing death or a serious adverse reaction, then only a few nutrients are of special concern. In everyday practice, vitamins A, D and B_6 require special attention, as do the minerals iron, zinc, copper and selenium. Obviously, effects are dose-related and, in some cases, the doses are so large that they cannot practically be achieved in real life (see Appendix 6).

Natural versus synthetic

It is often asked whether natural and synthetic vitamins differ, and whether one is superior to and safer than the other. At this stage, very little research has been conducted to compare natural and synthetic forms, but some investigation into vitamin E has been undertaken.

The biological activity of vitamin E is based on the 'fetal resorption–gestation' method in rats. Using this test, the minimum amount of vitamin E required to sustain fetal growth in pregnant rats is determined. In the case of

D-alpha tocopherol (RRR-alpha), which is considered to be the natural form, the highest activity is observed and therefore valued at 100%, whereas the biological activity of other vitamin E isomers has been estimated to be as low as 21% (Acuff et al 1998). Studies in humans have indicated that natural vitamin E has roughly twice the bioavailability of synthetic vitamin E; however, whether this also means that it has greater efficacy has yet to be clarified (Burton et al 1998).

It has also been speculated that the natural beta-carotene used in supplements, which is derived from algae and contains a mixture of carotenoids, may be safer and possibly more effective than synthetic beta-carotene.

RATIONAL USE OF SUPPLEMENTS

Nutritional supplements can never take the place of a balanced diet or provide all the health benefits of a whole food, but they can provide nutritional assistance and therapeutic effects in three different ways:

1. **Supplementation to correct a gross deficiency.** A patient presenting with clinical signs and symptoms of a nutritional deficiency will require nutritional counselling and possibly supplementation to quickly redress the situation (e.g. vitamin C supplementation and dietary education for patients with scurvy).
2. **Supplementation to address a subclinical deficiency.** A patient may not be presenting with overt clinical signs or symptoms of deficiency but may benefit from an increased intake of certain nutrients or food components to prevent disease or reduce the incidence of other adverse outcomes (e.g. maternal folic acid supplementation and gestational health and development).
3. **Supplementation to address symptoms not associated with nutrient deficiency.** A patient presents with symptoms or disease unrelated to nutritional deficiency, but evidence indicates that nutritional supplementation can provide health benefits. This describes the use of nutritional supplements in pharmacological doses to achieve a specific health-related purpose, much like a therapeutic drug (e.g. high-dose riboflavin supplementation for migraine prophylaxis or coenzyme Q10 supplementation in hypertension). Many more examples are found in the monograph section of this book.

TABLE 3.3 The Rational Use of Nutritional Supplements

Be informed and seek out unbiased information — do not rely on label claims, product information manuals or other commercial sources of information alone.
Know the common nutrient deficiency signs and symptoms.
Know the RDIs and where relevant suggested dietary targets.
Know the benefits and risks of nutrients at levels beyond RDI and upper-limit levels (ULs) that increase the risk of adverse effects.
Be able to detect inadequate dietary intakes or refer to a healthcare professional who can do so.
Ensure that all healthcare professionals involved in a patient's care remain informed of nutritional supplement use.
Take care with children, the elderly, and pregnant or lactating women.
Take care when high-risk medicines are being taken.
Take care with HIV, cancer and other serious illnesses. Know the manufacturer or supplier details.
Store medicines appropriately.

Table 3.3 provides a general guide for healthcare professionals when considering nutritional aspects of their patients' situation and nutritional supplementation.

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CHAPTER 4
INTRODUCTION TO AROMATHERAPY

The term 'aromatherapy' refers to the use of essential oils and is an aspect of phytotherapy (botanical medicine). Essential oils are volatile liquid substances extracted from plant material by a variety of methods. However, 'aromatherapy' is frequently associated with cosmetic products that often do not contain any essential oils, even though the term 'aromatherapy' is included on the labels and advertising material of such products. There are several definitions of aromatherapy. Hirsch, for example, defines it as 'the use of odorants as inhalants to treat underlying medical or psychiatric symptoms' (Hirsch 2001), but this definition does not mention essential oils or differentiate between essential and fragrant (synthetic) oils, which are not usually recommended for use in healthcare. In addition, for the administration method Hirsch refers only to inhalation. Thus, Hirsch's definition does not accurately define aromatherapy or describe the way it is practised. For the purposes of this chapter, aromatherapy is defined as follows:

> The controlled use of essential oils from named botanical sources using a variety of application (external) or administration (internal) methods to promote and support health and wellbeing using a patient-centred evidence based approach.
> *Dunning 2005*

In this context 'controlled' encompasses:

- quality use of essential oils (QUEO) (Dunning 2005), which is based on the principles of the Quality Use of Medicines (Department of Health and Aged Care 1999)
- qualifications and competence of practitioners
- accurate diagnosis
- appropriate selection of essential oils based on a thorough assessment, stating the botanical name of the plant and plant part from which the oil was extracted and evidence for use where possible, and the administration/application, dose and dose frequency method
- appropriate documentation, including adverse-event reporting when relevant, and monitoring the effects according to the aims of the treatment
- appropriate storage and handling of essential oils to reduce deterioration and oxidation and meet infection control and disposal standards
- regulatory standards, including scheduling, manufacturing and advertising processes.

HISTORICAL OVERVIEW

Use of essential oils is recorded in most ancient civilisations in healthcare, religion and cosmetics, and to enhance the environment. For example, the ancient Egyptians used them to embalm the dead as well as in healthcare. Almost all cultures used odorants, including plant oils, as preventative measures and to fumigate people and environments during illnesses, such as the plague. In the Middle East, Avicenna (AD 980–1037) is credited with developing the original steam distillation process for extracting essential oils. In the late 1800s, Chamerland undertook research into the antiseptic properties of essential oils and in the 20th century Cavel, who studied the antiseptic properties of 35 essential oils in sewerage cultures, extended Chamerland's work.

A great deal of modern research concerns the relationship between odours and emotional states, cognitive performance (Jellinek 1998/99, Svoboda 2002, Van Toller & Dodd 1988) and stress management. It also focuses on the management of common health problems, such as upper respiratory tract infection

(URTI) and acute and chronic pain, in a range of healthcare settings that include aged care, midwifery and acute care such as coronary care units. Often the research is conducted on isolated chemical components of the essential oil, which does not reflect usual aromatherapy practice.

René Gattéfosse is credited with coining the term 'aromatherapy'. After burning his hand in a laboratory fire, he immersed it in a vat of lavender essential oil, which reduced the pain, and his hand subsequently healed without scarring or infection. Gattéfosse went on to use essential oils in military hospitals in World War I. Essential oils also played a major role in wound care during World War II, where Dr Jean Valnet used them in military hospitals in Europe and IndoChina. Marguerite Maury is largely responsible for the popularity of essential oils in modern beauty care. She introduced aromatherapy into the UK in the 1960s, and her technique of using low doses of essential oils dispersed in a carrier oil and applied in a massage strongly influenced aromatherapy practice in the UK and Australia (Price & Price 1995). Research into the therapeutic application of essential oils is continuing in many countries in animal and human subjects.

AROMATHERAPY PRACTICE MODELS

There are three main aromatherapy practice models, which have implications for the administration/application method, dose, dose intervals and safety. Essential oils are often combined with other conventional and complementary therapies such as massage and acupressure.

MEDICAL AROMATHERAPY

This is also known as aromatic medicine or aromatology. It is used in France and increasingly in the UK, and there is growing interest in Australia. An education program encompassing the internal use of essential oils was recently approved by the Australian National Training Authority. Medical aromatherapy utilises the internal administration of essential oils via the oral, rectal and vaginal routes, as well as in dressings, ointments and fumigation. Only steam-distilled and expressed essential oils are used internally. In France prescribing for internal use is regulated and restricted to medically qualified doctors who have the relevant training. A pharmacist often formulates the prescriptions. Aromatherapists may work under the direction of a doctor. In some other countries, other practitioners can prescribe essential oils if they have the relevant qualifications.

SUBTLE AROMATHERAPY OR AROMACOLOGY

This is the German model of practice, which largely uses inhalation to influence psychological and spiritual states.

POPULAR, OR TRADITIONAL, AROMATHERAPY

Largely based on the UK model, this involves inhalation and massage. Touch, an essential aspect of massage, has its own health benefits, and this model uses topical application in massage, gels, creams and lotions, as well as inhalation for physical, psychological and spiritual effects. There are two subgroups: therapeutic aromatherapy, which is used in healthcare, and cosmetic or beauty care aromatherapy. Australian aromatherapists largely follow the UK model, but some incorporate aspects of all three models.

All three models use essential oils as the main medicinal substance. Essential oils are rarely used undiluted, but rather are incorporated into various carrier substances, depending on the administration/application route. Most aromatherapists formulate blends for individual patients, but fixed-formulation blends are available: for example, massage blends for pain relief. Aromatherapy is very popular with the general public and self-prescribing by following the directions in self-care books, magazine articles and short education courses is common. In Australia some health insurance funds reimburse the costs of aromatherapy treatments, provided the aromatherapist is qualified through an approved training facility.

ESSENTIAL OILS

CHEMISTRY

Essential oils are secondary plant metabolites and are complex chemical compounds that have a different composition from the herb extract of the same plant. Essential oils are stored in specific secretory structures in leaves, twigs, seeds, petals, bark and roots, often with resins and gums in oil cells, sacs, resin canals, ducts and hairs, and are extracted from these structures by steam distillation, expression, enfleurage, solvent extraction, maceration and more recently supercritical carbon dioxide

extraction, depending on the plant source (Guba 2002, Price & Price 1995). More than 3000 odour molecules have been identified.

Chemical variations are common in plants of the same genus and these are known as chemotypes. The best known chemotypes occur in the essential oils of *Thymus vulgaris* (thyme), *Rosmarinus officinalis* (rosemary), *Ocimum basilicum* (basil), and *Melaleuca alternifolia* (tea tree). Growing conditions, harvesting, storage and handling are known to affect the chemical composition of essential oils (Guba 2004, Price & Price 1995). Common phytochemicals in essential oils are terpenes, sesquiterpenes, alcohols, phenols, aldehydes, ketones, esters, acids, phenolic ethers, oxides, lactones and coumarins (Bowles 2003, Clarke 2002). It is necessary to understand the chemical composition of essential oils in order to understand their application in healthcare and the safety aspects associated with their use.

Of the many chemicals present, the alcohols, lactones, phenols and sesquiterpenes are considered to have a major impact on the odour of the oil and are of particular significance in the cosmetic and perfumery applications of aromatherapy. Of these chemicals, alcohols are considered to be among the most important for therapeutic effect and pleasant fragrance. They often have antimicrobial properties and low toxicity, and are described as warming, uplifting and good general tonics. Two examples of alcohols found in essential oils are:

- linalool, found in the essential oils of lemon, rosemary, sage, thyme and mandarin, and which has anaesthetic, antiseptic and sedative effects
- terpineol found in the essential oils of frankincense and tea tree, and which has antiseptic activity.

The sesquiterpenes consist of three isoprene units and make up the largest group of terpenes found in the plant world. They tend to have strong odours and a variety of pharmacological effects. Two examples of sesquiterpenes found in essential oils are:

- caryophyllene, found in oil of cloves, eucalyptus, ginger, lavender, marjoram, sage, thyme, ylang ylang and valerian. It has a strong spicy, woody odour and anti-inflammatory, antispasmodic, antibacterial, fungicidal and sedative effects.
- chamazulene, found in German chamomile, which gives it the characteristic blue colour. It has analgesic, anti-inflammatory, antioxidant, antiseptic and antipyretic effects.

Optical isomerism also influences the odour of a substance, so two different oils containing the same specific chemical may have different odours because the chemicals are stereoisomers. For example, *d*-limonene found in citrus oils, pine leaves and peppermint has a citrus odour, whereas its stereoisomer *l*-limonene has a turpentine-like odour and is found in citronella and lemon verbena.

Although the pharmacological effects of many of the constituents found in essential oils have not yet been fully investigated, a few that have been investigated are notable for their significant activity. For example, eugenol is a phenol found in cinnamon, oil of cloves and ylang ylang, giving the oils a spicy, pungent odour and significant antimicrobial activity. Cinnamaldehyde, chiefly found in cinnamon oil, has also been well investigated. It has antispasmodic, antimicrobial and fungicidal activities and is described as having a warm, spicy and balsamic odour.

Most of the essential oils produced are used in the food, cosmetic and, to a lesser extent, medicine industries, where strict composition standards are needed to ensure products meet relevant standards. Organisations such as the International Organisation for Standardisation (ISO), Research Institute for Fragrance Materials (RIFM), International Fragrance Association (IFRA) and Association Française de Normalisation (AFNOR) have developed composition standards for many essential oil products used in the food and perfume industries, and this is an important aspect of quality control. The ISO and AFNOR standards are often accepted as the most reliable indicators of quality.

The need to achieve compositional consistency has led some manufacturers to artificially manipulate chemical composition, using adulteration, substitution and rectification, to ensure essential oils meet the standard and to reduce the cost of expensive oils such as rose and jasmine. Plant conservation issues have also affected aromatherapy practice: for example, the sale of essential oils from some endangered species is banned in Europe. In some cases synthetic products have been developed, which may increase the potential to cause adverse events and bring aromatherapy into disrepute. The European Federation of Essential Oils was formed in 2002 to increase awareness of the need for sustainable harvesting to benefit both local communities and aromatherapy, as well as to conserve endangered plants.

Analytical techniques such as gas chromatography, mass spectrometry, infrared spectroscopy, optical rotation and refractive index are used to assess the composition and purity of essential oils. Frequently mass spectrometry and infrared spectroscopy are considered together. The analytical information, together with other safety information, is detailed in material safety data sheets, which are available from essential oil suppliers and manufacturers. More recently, the cosmetic industry has begun to examine the peroxide value (POV) of both essential and fixed vegetable oil carrier oils. POV is an indicator of the potential of an essential oil to cause skin irritation and sensitivity (Wabner 2002). In addition, the physical appearance (colour and consistency) and odour of the oil are important aspects of quality.

Currently, there is not a standard for 'therapeutic-grade essential oils' (Guba 2004). However, some suppliers undertake independent quality-control tests to ensure essential oils meet aromatherapy requirements and to guarantee that their essential oils are:

- 100% pure, which means they are not adulterated in any way
- 100% natural, which means they are made from plant material and do not contain any synthetic substances
- 100% complete, which means they are single-distilled and have not had any chemical constituents removed or added.

In Australia most essential oils are listed in schedule 14 of the medicines scheduling system of the Therapeutic Goods Administration (TGA). However, TGA listing does not necessarily indicate benefit or efficacy, but does indicate that the risks associated with listed products are low. Manufacturers are not permitted to make therapeutic claims for listed products.

Aromatherapists prefer to use the entire essential oils rather than isolated compounds or synthetic oils, because the chemicals present in individual essential oils and blends have synergistic and quenching properties that enhance the beneficial effects and reduce unwanted effects. These beneficial interactions occur among the individual constituents within an oil and among the essential oils in a blend of oils (Clarke 2002, Price & Price 1995, Opdyke 1976). In most cases a blend of essential oils is used to suit the condition being treated, and the composition of the blend is modified according to the individual's response in much the same way as herbal medicines are used. Common application/administration methods and doses are shown in Table 4.2 at the end of this chapter. Recommended doses are based on a long history of traditional use and the recommendations of experts, rather than on dose-finding trials. A number of factors need to be considered when deciding on an application method, dose and dose interval including:

- the aromatherapy model being used
- the pharmacokinetics and pharmacodynamics of the essential oils
- the mode of administration/application
- the patient's age and gender, presenting health issues and medical history, including allergies
- other conventional and herbal medicines being used
- the qualifications of the practitioner.

Most aromatherapists do not recommend using fragrant oils for therapeutic purposes, although most accept they may have a role as environmental fragrances and may have psychological effects.

CARRIER SUBSTANCES

In most cases essential oils are dispersed in another substance known as a carrier. Carrier substances for massage are usually cold-pressed or fixed vegetable oils, such as sweet almond, grapeseed and macadamia nut oil, depending on the aims of treatment. In massage, the carrier oils primarily provide lubrication for the therapist's hands to allow smooth movement over the skin and to enhance absorption of the essential oils; however, some fixed oils, such as those of calendula (*Calendula officinalis*) or St John's wort (*Hypericum perforatum*), also have therapeutic properties.

Other carriers include honey, *Aloe vera*, shea and cocoa butter, and waxes, which are used for capsules, ointments and suppositories intended for internal use. Purified clays such as bentonite are also used as carriers for essential oils to be applied in compresses, poultices and face and body masks/packs in beauty care. Incipients (dispersants) are usually required if essential oils are added to water to keep them in solution because essential oils are generally insoluble in water.

HYDROSOLS

A hydrosol is the condensed water co-produced with the essential oil during steam distillation (Catty 2001). Each litre of hydrosol contains low doses of essential oils, between 0.05 and 0.02 mL, depending on the solubility

of the constituents in the oil being distilled, the duration of the distillation process and the hydrophilic/lipophilic nature of the constituents. Therefore, the chemical profile is different from the essential oil obtained from the same distillation. Hydrosols can be used as carrier substances or prepared as tinctures, spritzers and compresses; frequently, they can also be drunk (Catty 2001).

PHARMACOKINETICS AND PHARMACODYNAMICS

Essential oils are absorbed, metabolised and excreted in a similar way to fat-soluble medicines (Tisserand & Balacs 1995). They have a short life span in the blood, from where they are distributed to muscle and adipose tissues over a longer period. They may bind to plasma proteins for transportation, and detoxification primarily occurs in the liver. The exact pharmacokinetics and pharmacodynamics depend on many factors, including the route of administration.

Research into the pharmacodynamics and pharmacokinetics of essential oils indicates that they are metabolised and excreted between 72 and 120 hours after administration/application depending on the:

- body size of the subject
- chemical composition of the essential oil/s carrier substance
- carrier substance
- application/administration route
- dose, dose form and dose interval
- individual's health status.

Essential oils are absorbed through the skin, but the absorption rate of the various chemical components in a particular essential oil depends on a number of factors, including the size of the individual molecules, the percentage of essential oils in the blend, total dose applied, the area covered and the state of the circulation. Jager et al (1992) detected linalool and linayl acetate (components of lavender) in the blood at 5 minutes after a 10-minute abdominal massage using 2% *Lavandula angustifolia* in peanut oil.

Likewise, salicylate was detected in subcutaneous tissue within 30 minutes and for up to 60 minutes after the application of 20% methyl salicylate to the forearm (Cross et al 1997). Larger molecules, such as the coumarins, take up to 1 hour to penetrate (Ford et al 2001). Covering the area after applying the essential oils enhances absorption. Absorption is usually rapid from the rectal and buccal mucosa. Gastrointestinal factors such as diarrhoea and vomiting can affect absorption of oral doses.

Research is currently under way to ascertain whether essential oils enhance the absorption of topically applied medicines. Components such as limonene, 1,8-cineole and nerolidol enhance the penetration of both hydrophilic and lipophilic substances (Cornwall et al 1996, Duke 1998). Such research suggests topical application of essential oils may be contraindicated or caution required if conventional topical medicines such as anti-anginal agents, nicotine patches or hormone replacement therapy (HRT) are used at the same time.

SAFE USE

Safe use of essential oils is a complex topic that includes similar issues to those concerning herbal medicine safety. It is largely based on the long history of safe traditional use, case reports and animal studies to determine lethal doses (e.g. LD_{50}). The lethal dose (LD) may not provide useful information about topical applications. Even less is known about effective doses (ED) or the effects of organ disease, such as liver, renal or cardiac disease, on the metabolism and elimination of essential oils, although it is reasonable to expect these would be important considerations for internal dosing, as would the state of the skin for absorption of topical applications. Safety information can be found in the essential oil material data sheets, *The complete German Commission E monographs* (Blumenthal et al 1998) and the *ESCOP monographs: The scientific foundation for herbal medicinal products* (ESCOP 2003), as well as Poisons Information Centres (see Appendix 3).

Common potential risks are:

- skin, eye and mucous membrane irritation to the person using the oils and people in the vicinity (this is also an occupational hazard for practitioners)
- phototoxicity
- local irritation
- allergy (regular use of the same essential oils increases the risk of cumulative effects and allergy)
- odours can trigger respiratory difficulties, asthma or migraines in susceptible individuals
- unwanted psychological effects (e.g. euphoria in people with dementia).

Essential oils that contain aldehydes, phenols and furocoumarins, especially citrus oils such as bergamot (*Citrus bergamia*), are more likely to irritate the eyes, mucous membranes and skin,

and cause sensitisation. Contact sensitisation related to monoterpene oxidation (Tisserand & Balacs 1995) is frequently the result of poor storage conditions (Burfield 2000). If a skin reaction occurs, the area should be blotted with tissue to remove or dilute the oils and a carrier substance applied and removed with tissue. The process may need to be repeated several times. Removing with soap and water may exacerbate the reaction (Bensouilah & Buck 2006). The reaction should be noted in the individual's health history and an adverse event notification filed depending on its severity.

Cross-sensitisation to other essential oil components and foods has also been reported: for example, between Thai food and *Cymbopogon flexuosus* (East Indian lemongrass) (Bleaser et al 2002, Clarke 2002). Perfume and fragrant products found in candles, aerosols, incense and soaps are common irritants and often contain limonene, coumarin, geraniol and cinnamaldehyde (Harris 2005). Some also contain carcinogenic substances such as styrene or naphthalene, and some contain formaldehyde in amounts many times the safe limit, which is < 2 micrograms/m^3 of air (Harris 2005).

Patch testing of susceptible individuals (e.g. those with atopy) is recommended. Allergy from inhaled essential oils is known to occur, but data about exposure levels are limited and many of the reports concern perfumes rather than essential oils (Burfield 2000). Cumulative effects can occur. Essential oils that are not commonly used in aromatherapy have been associated with cancer, neurotoxicity (ketones) and hepatoxicity in large doses in animals, and these adverse events are most likely to occur with internal use (Tisserand & Balacs 1995).

Potentially carcinogenic essential oils

There is no evidence that essential oils cause cancer in humans, although some constituents are potentially carcinogenic, particularly saffrole, iso-saffrole, estragole, methyl chavicol, methyl eugenol, elemicin, asarone and *d*-limonene (Tisserand & Balacs 1995). High doses and prolonged use of essential oils containing these constituents should be avoided; however, most of these are not commonly used in aromatherapy.

Use in pregnancy

Essential oils are widely used in midwifery units in Australia, the UK and USA. Women use them largely to manage backache, nausea, discomfort from varicose veins, prevent or reduce stretch marks, and reduce perineal discomfort. Essential oil massages are often used in the last trimester to relieve backache and to aid relaxation and mental wellbeing. In Australia there is little internal use of aromatherapy oils; however, the practice is starting to attract interest. Internal use of essential oils should be undertaken with caution in pregnancy, as there are a number of reports of adverse effects following oral ingestion or vaginal use. This may be because higher doses achieved with oral dosing are likely to reach the fetus, as the placenta is permeable to essential oils because of their small molecular size (< 500 molecular units). This does not necessarily represent a risk to the fetus, but the fetal liver may not be mature enough to detoxify the oils or their components. In contrast, there are no case reports of topically applied or inhaled essential oils causing harm, but there is also no definitive evidence confirming safety in the first 16 weeks of pregnancy. A low dose, ~ 2%, is therefore recommended for full body massage during pregnancy, based on expert opinion rather than definitive evidence.

Although there is good evidence that fetal organs and tissues are sensitive to different chemicals at different stages of development, no such data is available for essential oils (Tisserand & Balacs 1995). When deciding about the risks and benefits of using essential oils during pregnancy the woman's medical history, obstetric history, weeks of gestation, and current health need to be considered. Table 4.1 (p 42) shows essential oils that should be used with caution, those that should be avoided throughout pregnancy and those generally considered safe to use. Taking a cautious view, aromatherapy experts recommend that essential oils with the potential to cause fetal damage be avoided throughout pregnancy. Essential oils containing sabinyl acetate and apiol represent the greatest risk to the fetus. Essential oils with a high proportion of antheol have mild oestrogenic effects, therefore internal use of these oils is not recommended. Many aromatherapists recommend emmenagogue essential oils be avoided, although there is little scientific evidence to indicate they cause adverse outcomes when used topically or inhaled.

Some of the current recommendations are based on contraindications for the herb extract; however, as has already been pointed out, essential oils and herbs may contain very different chemical components, even when they are derived from the same plant. Until more is known, caution is recommended.

TABLE 4.1 Use of Essential Oils During Pregnancy

Generally considered safe	Generally safe to use externally	Use with caution	Avoid. These contain camphor, apiol, sabinyl acetate or pinocamphone
Cardamom Roman and German chamomile Clary sage Coriander Geranium Ginger Lavender Neroli Palmarosa Patchouli Petitgrain Rose Rosewood Sandalwood Sweet orange or mandarin	Anise Fennel Lavandin Lavender spike *Lavandula stoechas* Rosemary Star anise Yarrow Mace	Artemisia Cangerama Cotton lavender Oakmoss Perilla Rue	Camphor Ho leaf Hyssop Indian dill *Juniperus pfitzeriana* Parsley leaf Plectranthus Spanish sage Savin

INTERACTIONS

It is difficult to determine whether interactions between conventional medicines, herbal medicines and essential oils occur. Most texts focus on interactions with conventional medicines, and there is little information about interactions with herbal medicines. Interactions between topically applied essential oils and medicines are most likely if they are both applied to the same local site. Only very small amounts are absorbed from topical application, so clinically significant interactions are unlikely, but the potential for interactions increases with internal use (see Table 4.2 at the end of this chapter). The exact mechanism of actual or potential interactions is difficult to define. Most are theoretical, largely based on animal studies, and most are not thoroughly researched.

SAFETY PRECAUTIONS

Most available essential oils are considered safe and present few risks when used appropriately.

- Most essential oils should not be applied undiluted to the skin.
- Susceptible individuals, such as those with a history of allergies or eczema, can develop a sensitivity to any essential oil.
- The risk of serious adverse events is higher with internal administration methods, especially oral.
- Essential oils containing aldehydes and phenols are more likely to cause allergic reactions. Patch testing before using essential oils for the first time may be indicated, especially in at-risk individuals.
- Using the same essential oils for long periods may lead to cumulative effects and cause sensitivity after a period of time. After 3 weeks of use, cessation for at least 24 hours is recommended.
- Although there is not any quality evidence to support recommendations for the use of essential oils in certain groups of people, traditional precautions and contraindications concerning pregnancy and lactation, epilepsy, asthma, people with alcohol or other addictions, certain age groups and disease states should be considered.
- Use traditional doses and dose intervals. Most aromatherapists use low doses, although effective therapeutic doses and dose ranges for specific situations are unclear.
- Some essential oils are not used in aromatherapy because of their known toxicity: for example, wormwood, rue, camphor, bitter almond and sassafras. Oil of wintergreen is sometimes on the exclusion list, but if it is used appropriately, it is an effective analgesic in a massage blend for muscular aches and arthritic pain.
- Essential oils must be appropriately stored and kept out of the reach of children, the cognitively impaired or suicidal patients to avoid inadvertent or deliberate overdose. Vaporisers should also be placed out of reach.
- Essential oils are highly flammable. Products must be used and disposed of appropriately to reduce the fire risk.
- Educating patients who self-apply essential oils is an important aspect of safe use.

For safety and medicolegal reasons healthcare professionals and the general public are advised to buy essential oils from reputable sources that label and store their products correctly. Labels are an important source of information and should contain the following information:

- botanical name, species, and if relevant the chemotype of the plant from which the oil was extracted or, in the case of a blend, for all the oils in the blend
- part or parts of the plant from which the essential oil was extracted
- country where the plants were grown (country of origin)
- extraction method
- statement of purity (However, this is not a regulatory requirement and not all suppliers make such statements.)
- batch number, so that the batch can be identified if an adverse event occurs to determine whether the reaction was idiosyncratic or occurred because of the manufacturing process
- expiry date and storage precautions
- in some cases specific warnings: for example, phototoxicity risk in Australia
- supplier details.

STORAGE

Essential oils are volatile and readily evaporate, so they should be stored in airtight amber glass bottles to protect them from light and air. Plastic is usually avoided because there can be transference of chemicals in the oil to the plastic and vice versa, thereby changing the chemical composition of the oil. Essential oils should also be stored in a cool place, preferably away from direct sunlight. Some aromatherapists store oils in a refrigerator. The 'top notes' of the oil have the lowest boiling points and are highly volatile and evaporate first, thereby altering the aroma of the oil. In general, oils should be used within 1 year of opening; however, their shelf life can be extended with careful use and storage.

AROMATHERAPY IN PRACTICE

The level of evidence for aromatherapy use is an important aspect given the current focus on evidence-based care. The level of evidence is judged according to the quality of the research, considering factors such as statistical power, study design, accuracy of the measurements, and the outcomes. Overall, most clinical aromatherapy research is low-level evidence (DANA-Farber Cancer Institute 2008). In addition, individual practice varies considerably, which means that the management of specific health conditions varies considerably.

As with all clinical practice, it is important to be clear about the goals of treatment and decide what treatment/s and forms of administration will achieve those goals. For aromatherapy, this means choosing the correct essential oils and whether the topical and/or inhaled method of administration is suitable. Psychological, physical and practical requirements are also assessed, together with relevant safety information. When using oils topically in children, the elderly or allergenic people, it is recommended that a skin test be performed first. One drop of oil applied with a cotton ball or swab to the inside of the elbow or wrist is usually sufficient. The application area should be marked and left unwashed for 24 hours. If a reaction occurs (redness and itch) the offending oil should be avoided. See Table 4.2 at the end of this chapter for more information about using oils in practice.

CHOOSING AN AROMATHERAPIST

Aromatherapy may be particularly beneficial for managing stress and inducing relaxation. It can also be useful in skin care, for managing topical fungal and bacterial infections, to relieve respiratory symptoms, as topical analgesia, and to reduce muscle spasm, especially when combined with massage. A key aspect of safe, effective aromatherapy treatment is choosing a knowledgeable and competent aromatherapist.

Education and competence

The aromatherapist should belong to a professional association, such as the International Federation of Aromatherapists (IFA) or the Australian Aromatic Medicine Association (AAMA), that has defined membership criteria, including the expectation that the aromatherapy training curriculum was approved by the Australian National Training Authority and/or state training authorities, whose competencies are consistent with national competency standards for aromatherapy, continuing professional development requirements and a code of professional conduct. These associations maintain membership lists and can be accessed via the telephone directory or their respective websites. Aromatherapists in Australia are not regulated, but membership of such

TABLE 4.2 Common Application Methods, Recommended Doses and Safety Tips for Essential Oils

Application method	Doses (using a standard essential oil dropper top)	Safety tips
Massage	*Adults* The recommended dose is between 3.5% and 5% of an essential oil blend in a carrier oil. However, larger doses can be used safely (e.g. 15% in an aqueous cream, 10% in a gel). The dose also depends on the presenting problem (e.g. undiluted tea tree or lavender oil might be applied to an insect bite or a small burn, whereas lower doses would be used for chronic diseases). *Children* Children > 7 years and the elderly: 1–1.5%. Children 2–7 years: 0.5%. *Babies* 0–1 year: no essential oils. Approximately 25–30 mL of a carrier substance is needed for a full adult body massage, depending on size of the individual, skin condition and amount of body hair.	• To avoid cumulative effects and reduce the likelihood of sensitivity developing over time, the same essential oils should not used for long periods. • Essential oils containing aldehydes, phenols and furocoumarins, especially cinnamon (or cassia) and citrus oils such as bergamot (*Citrus bergamia*), are more likely to irritate the eyes, mucous membranes and skin, and cause sensitisation. • Geranium, ginger, pine and citronella should be avoided by people with sensitive skin or a history of dermatitis. • Essential oils are not recommended for use on babies.
Bath	4–7 drops of essential oils added to a warm bath directly or first mixed in a carrier substance and agitated into the bath water.	• Take care that bath water with oils is not ingested and does not enter eyes. • The oil must be mixed into the water before the person gets into the bath, not left floating on the surface.
Vaporiser	4–7 drops applied onto the surface of the water that is to be vaporised.	Keep vaporisers out of the reach of children and confused people who might drink from them. Poisoning has been reported in children drinking from vaporisers.
On a tissue, cotton ball, pillowcase or clothing	1–2 drops applied directly and inhaled from these items.	
Steam inhalation	Fill a bowl with 2 cups of almost boiling water and add 2–4 drops of essential oils. The scented steam should be inhaled for 5–10 minutes. Low doses of essential oils should be used to reduce the risk of irritating the respiratory mucous membranes and the eyes, especially when the oils are highly volatile (i.e. top notes). Five drops of essential oil yields approximately 35 mg of essential oil from a nebuliser.	• Take care with people who have asthma because some oils can exacerbate symptoms. • High doses, and some essential oils such as eucalyptus, can irritate the eyes.
Unscented lotions, creams or ointments	4–5 drops/60 mL of vehicle such as aqueous cream, white soft paraffin or vitamin E cream.	
Gargle and mouth wash	2–3 drops in 30 mL of distilled or spring water; for children, 1 drop mixed in honey before adding to water. Hydrosols can be used as mouthwashes and gargles.	Not to be ingested orally.
Room sprays and spritzers	8–10 drops in 500 mL of distilled water. Spritzers are useful when the person cannot be massaged (e.g. for herpes zoster 15–20 drops in 50 mL can be used to relieve pain and itch). Hydrosols can be used as spritzers.	• Use glass bottles or stainless steel spray cans, not plastic containers. • Do not spray into the eyes.

Continued

TABLE 4.2 Common Application Methods, Recommended Doses and Safety Tips for Essential Oils *continued*

Application method	Doses (using a standard essential oil dropper top)	Safety tips
Poultice	2–3 drops in ½ cup of chopped up solid or semi-solid medium, e.g. clay, oatmeal, linseeds, chopped comfrey. Hot water can be added to the mixture to make a paste, which is then spread onto a piece of gauze and covered with a second piece of gauze. Fold over the ends to secure the contents and apply warm to the affected area.	
Compress — hot or cold Cold compresses are used when there is inflammation, swelling or headache; hot compresses for muscle aches and pains, menstrual pain or boils.	2–6 drops, depending on the size of the area to be covered by the compress: 2–3 drops for a finger; 5–6 drops for a knee. A soft piece of fabric (e.g. flannel, towelling) is sufficient for both types. Put 6–10 drops of essential oil into 0.5 litre of water (ice-cold or hot) and place the fabric on top of the water. Squeeze the fabric to prevent it from dripping when lifted out; however, don't allow the fabric to become too dry. Place the compress on the area to be treated and reapply when it has warmed or cooled to body temperature.	
Undiluted on the skin (tea tree, lavender)	1–2 drops onto a cotton bud and applied directly to the affected area.	• Essential oils should not be applied directly to the skin unless under the direction of an aromatherapist. • Some low-irritant essential oils, such as lavender and rosewood, are generally safe.
Oral, buccal (not generally used in Australia or New Zealand)	30 mg/dose for adults in a gel, capsule or lozenge. *Acute conditions* 60 mg three times daily for 3 days. *Chronic conditions* 30–45 mg three times daily for 15 days.	• Essential oils should be used orally only under the direction of an aromatherapist qualified in this method of use. • Many essential oils irritate mucous membranes.
Rectal suppositories (not generally used in Australia or New Zealand)	*Adults* 150–450 mg/day three times daily for 3 days. *Chronic conditions* 150 mg/day for 15 days.	• Essential oils should be used only under the direction of an aromatherapist qualified in this method of use. • Many essential oils irritate mucous membranes.
Vaginal suppositories (not generally used in Australia or New Zealand)	150 mg on 1 g suppository. 1–5% with an excipient in a douche. Up to 10% in a carrier substance on tampons.	• Essential oils should be used only under the direction of an aromatherapist qualified in this method of use. • Many essential oils irritate mucus membranes.

an association suggests self-regulatory processes are in place. Undertaking short courses is adequate for self-care, but not for the therapeutic application of essential oils, even by healthcare professionals such as doctors and nurses.

Professional courtesy

The aromatherapist should communicate with other relevant healthcare providers, document the care provided, including monitoring outcomes and adverse events, provide advice that includes the benefits and risks of using essential oils, and recommend that people with serious conditions seek medical advice.

Safety

The aromatherapist should adhere to relevant occupational health and safety standards and other relevant Acts and regulations: although aromatherapists are not regulated, regulations apply to the products they use and their premises.

Clarity of outcome

The aromatherapist should be clear about what aromatherapy can offer and their personal competencies.

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CHAPTER 5
INTRODUCTION TO FOOD AS MEDICINE

Let food be your medicine and medicine be your food. (Hippocrates)

The maxim coined by Hippocrates, the father of Western medicine, around the 5th century BC, is as true today as it was then. Hippocrates observed that certain foods had the potential to both prevent and treat disease, and recognised the effects of nutritional deficiencies and excesses on health (Jensen 1993). Hippocrates' axiom went largely ignored in the evolution of Western medicine, but the pioneering work of researchers such as Linus Pauling and Victor Rocine in the early 20th century created a renewed interest in the therapeutic value of food and its influence, both positive and negative, on health.

Over the last 100 years a number of significant developments have been made in nutritional science, including:

- identifying essential nutrients and documenting their associated biochemical pathways
- defining nutrient reference values and RDI required to prevent nutritional deficiencies
- establishing dietary guidelines that include increasing consumption of fruits, vegetables and fibre, and reducing fat
- developing food guides, such as food pyramids, that can be used for daily meal planning.

Nutritional science has also led to the recognition that diet plays a major role in the chronic diseases that cause the bulk of morbidity and mortality in modern societies, such as heart disease, diabetes, hypertension and cancer.

Together with an increasing understanding of the potential benefits and negative consequences of food choices comes an unprecedented availability of different foods. Yet despite this, a problem of oversupply has arisen in developed countries and many Australians are consuming vast amounts of kilojoule-laden, yet nutrient-deficient, foods resulting in nutritional depletion and suboptimal nutrition. Largely as a result of this phenomenon, nutrition research has shifted from focusing exclusively on deficiency states to investigating the association between disease prevention, healthy ageing and adequate dietary intake in order to optimise quality of life and long-term health (Kennedy 2006).

FUNCTIONAL FOODS

The foods and substances we ingest affect us even at the most basic cellular level. In recent years scientists have discovered many thousands of previously unidentified substances in food and described their therapeutic actions. Currently around 50,000 (of a likely 200,000 substances) have been identified and described, yet for the most part we know very little about their functions (Hounsome 2008). These substances are known as phytonutrients, phytochemicals or a-nutrients. They impart colour, taste and smell, as well as possessing therapeutic properties such as antioxidant, anticarcinogenic, antimicrobial, antihypertensive, anti-inflammatory and cholesterol lowering properties. Major classes of phytonutrients include phenolic and polyphenolic compounds (flavonoids, phenolic acids, lignins), terpenoids (carotenoids, tocopherols and tocotrienols, quinines, sterols), alkaloids (including saponins), and sulfur-containing compounds (glucosinolates) (Goldberg 2003). A brief summary of some of the better known phytonutrients, their major actions and therapeutic uses is shown in Table 5.1 (pp 48–50). Although thousands of studies have already been conducted to identify phytonutrients in foods and understand their properties and influence on human health, much remains unknown.

TABLE 5.1 Examples of Phytonutrients Found in Functional Foods and Their Main Actions and Uses

Class/Phytonutrient	Main food sources	Main actions	Clinical use
Carotenoids			
Beta-carotene	Carrots, sweet potatoes, spinach, pumpkin, apricots, rockmelon (cantaloupe)	Anticarcinogenic Antioxidant	May reduce the risk of lung cancer in smokers. May protect against UV radiation (Stahl et al 2006).
Lutein, zeaxanthin	Green leafy vegetables such as kale, chard, spinach Egg yolk	Antioxidant Antitumour (breast, colon)	May reduce the risk of macular degeneration and cataracts, cardiovascular disease and some cancers (Ribaya-Mercado & Blumberg 2004).
Lycopene	Tomatoes cooked with oil, watermelon, guava, pink grapefruit, papaya	Antioxidant Anticarcinogenic (bladder, breast, cervix, prostate) Anti-inflammatory Hypocholesterolaemic	May reduce the risk of some cancers (especially prostate) and atherosclerosis (Bhuvaneswari & Nagini 2005).
Thiols/dithiols			
Alpha-lipoic acid (dithiol)	Potato, spinach Liver	Hypoglycaemic Antioxidant (water & lipid soluble) Hypotensive	May assist in the prevention of diabetic complications and cardiovascular disease. Recycles other antioxidants (Eddey 2005, Smith et al 2004, Wollin & Jones 2003).
Glutathione (thiol)	Garlic, fruits, vegetables Meat (found in all cells of plants and animals)	Antioxidant Chemoprotective	Important endogenous antioxidant
Phenolic compounds (including flavonoids)			
Phenolic acids	Most fruits and vegetables, especially the cruciferous (cabbage) family, tomatoes, berries	Antioxidant Anti-inflammatory Inhibits platelet activity	
Polyphenols	Fruits and vegetables Wine Green tea Extra-virgin olive oil Dark chocolate and other cocoa products	Anti-allergenic Antioxidant Anti-inflammatory	
Anthocyans (anthocyanins, glycosides, and their aglycons, anthocyanidins)	Fruits and berries	Anticarcinogenic Antioxidant	May reduce the risk of cancer (Cooke et al 2005).
Caffeic acid (phenolic acid)	Fruits (apples, pears, citrus) Some grains and vegetables	Antioxidant Antihypertensive Antithrombotic Antitumour Antiviral	May contribute to maintenance of healthy vision and cardiovascular health (Jiang et al 2005).
Ellagic acid (polyphenol)	Fruits, nuts and vegetables (e.g. strawberries, raspberries, grape seeds, onions)	Aldose reductase inhibitor (Duke 2003) Anticarcinogenic (cervix, colon, oesophagus, mouth) Antioxidant	Counteracts synthetic and naturally occurring carcinogens (Stoner & Mukhtar 1995).

TABLE 5.1 Examples of Phytonutrients Found in Functional Foods and Their Main Actions and Uses *continued*

Class/Phytonutrient	Main food sources	Main actions	Clinical use
Phenolic compounds (including flavonoids) *continued*			
Proanthocyanidins (catechin and epicatechin)	Fruits (e.g. apples, pears, grape seeds and peaches) Vegetables, nuts, beans Seeds, flowers and bark (e.g. pine) Tea Cocoa, chocolate	Antioxidant	May stabilise capillary walls and enhance wound healing. May assist in the treatment of pancreatitis.
Quercetin	Onions, beans Red wine Green tea, black tea Apples, berries	Anti-allergic Anti-inflammatory Antioxidant Antiviral	May assist in the treatment of allergies. May prevent diabetic complications.
Resveratrol	Red wine and red grape juice	Anticarcinogenic (breast, prostate, skin (Duke 2003)) Antifungal Anti-inflammatory Antioxidant Antithrombotic	May reduce risk of cardiovascular disease and cancer (Fremont 2000).
Diphenols (phyto-oestrogens)			
Isoflavones (daidzein, genistein, glycitein)	Soybeans and soy-based products	Anticarcinogenic (breast) (Duke 2003) Antioxidant Phyto-oestrogenic	May ameliorate menopausal symptoms and contribute to the maintenance of bone and cardiovascular health.
Lignans	Flax/linseed Some legumes and grains	Anticarcinogenic Antioxidant Phyto-oestrogenic	May contribute to maintenance of cardiovascular and immune function. May reduce risk of breast and prostate cancers.
Isothiocyanates			
Sulforaphane	Broccoli (especially young), broccoli sprouts, cauliflower, cabbage, kale, horseradish	Anti-apoptotic Anticarcinogenic Antioxidant	May reduce the risk of cancer (Fimognari et al 2005, Gills et al 2005).
Indoles			
Cruciferous indoles (indole-3-carbinol)	Cabbage, broccoli, Brussels sprouts, Chinese cabbage, Chinese greens, kale	Anticarcinogenic	May induce the metabolism of a cancer-preventative form of oestrogen and reduce the risk of cancer.
Fatty acids			
Conjugated linoleic acid	Dairy products and cooked meats	Anticarcinogenic Anti-inflammatory	May assist with fat loss and cardiovascular disease prevention (Eddey 2005).
Monounsaturated fatty acids	Olives, olive oil Canola oil	Anti-atherogenic Antihypertensive Anti-inflammatory	May reduce risk of cardiovascular disease and diabetes (Eddey 2005).
Omega-3 PUFAs (ALA, DHA, EPA)	Fish (deep sea/cold water) Flax/linseed, walnuts	Anti-arrhythmic Anticarcinogenic Antihypertensive Anti-inflammatory Cardioprotective	May reduce risk of cardiovascular disease (Eddey 2005). May contribute to maintenance of mental and visual function. Has many other uses.

Continued

TABLE 5.1 Examples of Phytonutrients Found in Functional Foods and Their Main Actions and Uses *continued*

Class/Phytonutrient	Main food sources	Main actions	Clinical use
Dietary fibre			
Beta-glucan	Oat bran, wholegrain oats	Antihypertensive Hypocholesterolaemic	May reduce risk of cardiovascular disease. Reduces GI of meal.
Insoluble fibre	Wheat bran, celery, dried beans	Anticarcinogenic	May contribute to the maintenance of a healthy digestive tract. May reduce the risk of colon, lung, breast, cervical cancers.
Soluble fibre	Psyllium seed husk, pectin, oat bran, broccoli	Hypocholesterolaemic Modulates bowel function.	May lower cholesterol and reduce risk of cardiovascular disease. May improve gastrointestinal health.
Prebiotics/probiotics			
Inulin, oligofructose	Globe artichoke, garlic, onions, leeks, asparagus Whole grains Some fruits Honey	Anti-inflammatory Modulates immune function. Prebiotic	Stimulates colonic production of short-chain fatty acids and favours the growth of lactobacilli and/or bifidobacteria (Guarner 2005). Increases calcium and magnesium absorption. Influences blood glucose levels and reduces the levels of cholesterol and serum lipids (Lopez-Molina et al 2005).
Lactobacilli/bifidobacteria	Yoghurt; some other fermented foods	Probiotic	May reduce diarrhoea (Bergonzelli et al 2005). Improves gastrointestinal health and systemic immunity.

Note: Data adapted from International Food Information Council 2005 and Duke 2003. See respective monographs for more detail.

In parallel with the advances in nutritional science, there has been growing consumer interest in food's potential to have a positive impact on health and wellbeing, as well as in developments in food technology that allow foods to be produced, processed, preserved and fortified so as to maximise their nutritional values. This has led to changes in food-labelling laws that permit certain foods to make claims about health benefits and has given rise to the development of functional foods.

The concept of a 'functional' food originated in Japan and is now being further developed, mainly in Japan, the United States and Europe. Functional foods are foods or dietary components that provide a health benefit that goes beyond their nutritional value, such as improving wellbeing and/or reducing the risk of disease. These may include traditional foods that have been shown to impart a positive biological effect or foods that have been modified to impart health benefits. Other terms that are used for functional foods are super foods, designer foods, fortified foods, nutraceuticals, cosmaceuticals, medifoods, vitalfoods and Foods for Specified Health Use (FOSHU) (Ashwell 2002).

Functional foods can be foods in which a component has been enhanced through special growing conditions or foods in which a component has been added, removed, modified or had its bioavailability increased. Functional foods cannot be marketed as medicines because they cannot make therapeutic claims for treating specific diseases; rather they are designed to be marketed to healthy consumers to enhance health and prevent disease (Ashwell 2002). As such, functional foods are distinct from dietetic foods, which are designed for treating illness and are marketed to health professionals.

Examples of functional foods include yoghurt and probiotics, vitamin- and mineral-fortified breakfast cereals, iodised salt and sports drinks (which are proven to promote rapid gastric emptying and fast intestinal absorption, to improve water retention, thermal regulation and physical performance, and to delay fatigue)

(Ashwell 2002). Many commonly prescribed 'herbal medicines' can also be considered as functional foods and are commonly used for both medicinal and culinary purposes. Many of these foods and food derivatives are included in the monographs in this book: for example, celery seed, chamomile, cloves, cranberry, dandelion, fenugreek, fish oils, garlic, ginger, green tea, honey, horseradish, lemon balm, liquorice, linseeds, noni, oats, peppermint, probiotics, raspberry, rosemary, sage, stinging nettle, thyme and turmeric.

Although functional foods retain their identity as foods and do not include pills, the line between food and medicine is a fine one and the line between food and herbal medicine even finer. In Australia, foods (including herbal medicines) are regulated according to their intended use either by the TGA or by Food Standards Australia New Zealand (FSANZ 2006). Recently, recognition of the therapeutic value of foods has led to a review of the extension of permissible health claims, substantiated by scientific evidence, that are allowed on food packaging. Regulations currently allow for nutrient-content claims (e.g. 'high in fibre') and some health-maintenance claims. Other types of health claims, with the exception of claims about the benefit of maternal consumption of folate, are prohibited (FSANZ 2006).

Although the primary aim of altering foods to make them 'functional' is to promote their beneficial effects, consideration should also be given to the potentially negative implications of manipulating foods, such as altering the natural synergy of nutrients, the introduction of synthetic nutrients and the possibility of detrimental effects. In the USA, for example, mandatory fortification of cereal and grain products with folic acid has raised concerns about masking the haematological abnormalities of vitamin B_{12} deficiency, thereby allowing the progression of neurological complications to continue undetected (Rothenberg 1999), as well as placing some individuals at risk of exceeding the recommended safe upper limit of 1000 micrograms synthetic folate daily (Jamison 2005), while still failing to meet the peri-conceptual requirements of others (see *Monographs: Folate*).

SUPPLEMENTS VERSUS FOOD

The actions of a whole food cannot be completely understood by studying its various components in isolation, because phytonutrients often interact with one another and, when used together, can produce different outcomes from those predicted for an isolated compound. Thus supplementation with individual food components may produce different effects from those produced by the consumption of the whole food. For example, epidemiological studies supporting the use of foods containing beta-carotene for the prevention of lung cancer in smokers have not been supported by clinical trials of supplementation with synthetic beta-carotene (Ziegler et al 1996) (see *Monographs: Beta-carotene*). Similarly, there is strong evidence to suggest that eating a variety of fibre-rich foods is beneficial in the prevention and management of diabetes; however, studies using fibre supplements have produced contradictory results (Venn & Mann 2004).

The results of these and other studies substantiate the value of 'whole foods' as medicine and suggest that epidemiological studies supporting the use of certain foods cannot necessarily be extrapolated to confirm the benefits of isolated supplementary nutrients. Furthermore, the practice of refining foods and then enriching them with synthetic versions of some of the lost nutrients cannot be deemed to be the equivalent of the whole food. Additionally, some nutritional supplements may not produce the desired or anticipated effect because of the absence of significant but as yet unidentified co-factors that are important for bioavailability, pharmacological activity or safety of the individual constituent.

Alternatively, nutritional supplements may prove life saving in an overt deficiency state and may enhance the individual's nutritional status when dietary intake is insufficient to meet physiological requirements, such as during periods of increased biological demand. Many of the isolated nutritional supplements discussed in this book are not only used to correct a deficiency state, but also have direct pharmacological activity at doses unattainable through dietary modification alone.

INDIVIDUALISING FOOD

An old Chinese proverb states 'Whatsoever was the father of disease, an ill diet was the mother'. Traditional medicine systems such as traditional Chinese medicine (TCM) and Ayurvedic medicine continue to understand and practise using food as medicine, and view food within a conceptual framework that includes the energetic value of food in addition

to its physical qualities. An assessment of different foods may be based on the food's 'vitality' or 'life force', otherwise known as 'chi' in TCM and 'prana' in Ayurvedic medicine. The type of food and its biological, nutritional and sensual properties, together with the many agricultural practices, production processes and preparation methods, make a contribution to this force. Every step in the process of producing a food may potentially affect the energetic value, net nutritional content and overall therapeutic benefits.

In traditional medicine systems, foods may be classified as having properties such as 'heating', 'cooling', 'drying' or 'moistening', and may be considered to be energetically aligned with one or more of five phases of transformation, or 'elements', that correspond to the different organ systems and tissues within the body, as well as to the different emotions, seasons, colours and so on. These properties, as well as constitutional typing of the patient, may be used to make a sophisticated assessment of an individual and to design dietary prescriptions that are based on an individual's constitution, propensities for disease development and/or responses to different foods. Thus traditional medicine systems can be seen to practise 'nutriphenomics', whereby a food is used as a medicine based on a person's phenotype.

Biomedical science has not matched the same degree of sophistication in individualising diet as traditional medicines; however, it is moving in this direction. Just as in pharmaceutical medicine the emerging science of pharmacogenomics promises to provide drugs best suited to a person's genetic makeup, the emerging science of nutrigenomics promises to deliver an understanding of how different nutrients affect genes to cause specific conditions and the ability to design foods and dietary recommendations based on an assessment of an individual's genotype (see also Chapter 3).

The increasing individualisation, complexity and knowledge base of nutritional science has led to research into 'Point-Of-Sale Individualised Foods' (POSIFoods), which integrate advances in nutritional science, innovative food processing and formulation processes and state-of-the-art vending technology to deliver fast, palatable and nutritious foods, tailored to an individual's dietary needs and taste preferences at the touch of a button (Decision News Media 2004). The success of such developments and their impact in human health, however, are yet to be determined.

FOOD QUALITY ISSUES

The health benefits of different foods must be considered in relation to the many agricultural farming practices and production processes that are involved. As soon as produce is picked or an animal is killed, it starts to decompose and lose nutritional value. When a ripe organic apple is picked in season directly from the tree and eaten immediately, its nutritional value is at its maximum. How does this compare to the apple grown in nutritionally depleted soil, using pesticides and herbicides, out of season, picked before ripening and kept in cold storage to extend its shelf life, potentially for months, even years?

Every step in the process, from paddock to plate and beyond, may potentially affect the nutrients, as well as the 'energetic' quality and therapeutic benefits of the food. Thus food quality can be affected by multiple factors:

- farming conditions, which include genetic variety, chemical exposure, maturity at harvest, location, water availability, soil composition, climate, seasons, aspect and sunlight exposure
- transport conditions and processing, such as milling, refining and enriching
- preservation methods, which may include chemical additives, cold storage, drying, salting, irradiation
- the conditions and length of storage
- meal preparation methods, such as cutting, crushing or tossing
- cooking methods, such as no cooking (i.e. food is raw), steaming, frying, microwaving
- how food is consumed, which includes duration of mastication, food combinations and the biochemical individuality of the person consuming the food (Gliszczynska-Swiglo et al 2005, Jeffery et al 2003, Podsedek 2005).

PESTICIDE RESIDUES

The creation of a global food industry and the emergence of agribusiness have led to the increasing use of pesticides in food production. At the same time there is growing worldwide public concern about the impact of these pesticides on human health. Currently, it is reasonable to expect that most animals on the planet have accumulated pesticide residues through water, air or the food chain and, although acute effects of pesticides are well documented, the chronic effects of pesticide exposure are more difficult to assess. A recent systematic review examined

the peer-reviewed literature published between 1992 and 2003 on currently used pesticides (the 'older' organochlorine pesticides were excluded) and their effect on human health. The review found that there is a high level of consistency across multiple studies to indicate a wide range of pesticide-related clinical and subclinical health effects, including significant positive associations between pesticide exposure and solid tumours (such as cancers of the brain, breast, kidney, prostate and pancreas) and haematological cancers (such as non-Hodgkins lymphoma and leukaemia); genotoxic effects; as well as effects on mental and emotional functioning, the nervous system, neurodegenerative diseases and reproduction (including birth defects, fecundity, fetal death and intrauterine growth retardation) (Sanborn et al 2004). A further review of the effects of pesticides on children indicates that pesticide residues have been implicated in causing reproductive problems, including miscarriages and spontaneous abortion, birth defects, childhood cancer, and neurological, neurobehavioural and endocrine effects (Garry 2004).

Children appear to be particularly vulnerable to the effects of pesticides because they eat and drink more per kilogram of body weight than adults, and their diets are often rich in foods that contain higher levels of pesticides, such as fresh fruits, vegetables and juices. It should be noted that such contaminants are often bio-accumulated in the fatty tissue of animals, and that concerns over pesticide exposure should not lead to the removal of nutrient-rich foods from the diet but rather to minimising exposure by choosing organic foods whenever possible.

Children's exposure to pesticides may also be increased through breastmilk. This provides many immunological, physiological, nutritional and psychological advantages, but is nevertheless commonly contaminated with high levels of pesticides. For example, it has been found that serum concentrations of organochloride compounds are significantly higher ($P < 0.0001$) in breastfed infants than in bottle-fed infants (Lackmann et al 2004), and that an infant's measured intake of organochlorines from breastmilk may greatly exceed the adult acceptable daily intake (ADI) (Quinsey et al 1995, 1996). In addition, children have less developed detoxification pathways; for example, newborn infants have low levels of the enzyme paraoxonase–1, which detoxifies organophosphate pesticides (Chen et al 2003). The fact that children born today have a longer life expectancy in which to develop diseases with long latency periods places them at further risk (Sanborn et al 2004). These factors led to the 1996 revision of the US Federal Fungicide, Insecticide and Rodenticide Act to include an additional 10-fold margin of safety for exposure to pesticide chemical residues in infants and children (Makris & Rowe 1998).

The dietary exposure of the Australian population to pesticides and other food contaminants was previously monitored every 2 years via the Australia Total Diet Survey (ATDS) conducted by Food Standards Australia New Zealand (FSANZ). The most recent surveys, however, have not included pesticides. The most recent to do so was the twentieth survey in 2003, which concluded that the levels of pesticide residues and contaminants found in Australian food sources were very low and within acceptable safety limits (FSANZ 2003a). The survey selected specific 'contaminants' for study and therefore cannot demonstrate broad effects on public health. Residue testing is also conducted on fresh produce in Australia (e.g. FreshTest and the National Residue Survey), but this is largely funded and directed by industry bodies.

Although safety assessments are conducted on pesticides and guidelines are set for maximum residue levels (MRLs), this does not necessarily guarantee food safety as numerous other factors need to be considered. Safety assessments usually examine only single chemicals at high doses and often only in animals, which may lead to a significant underestimation of the potential risk associated with the numerous mixtures of compounds that consumers are typically exposed to. The combined toxic effect of multiple chemicals is not necessarily predictable by adding up the toxic potential of each chemical; mixtures of chemicals can also interact to produce synergistic toxic effects. Thus it is possible that there may be greatly enhanced toxicity of these compounds when they are combined, and this is supported by research documenting reproductive, immune and nervous system effects not expected from the individual compounds acting alone (Boyd et al 1990, Porter et al 1993, 1999, Thiruchelvam et al 2000). Pregnant and lactating women require specific consideration to minimise exposure of the fetus or infant during critical periods of development, and children do not metabolise chemicals as efficiently as adults (Sanborn et al 2004).

GENETIC MODIFICATION (TRANSGENIC FOODS)

Conventional methods of selective breeding and cross-breeding have been used for centuries to alter the genetic makeup of the foods we consume; for example, the wheat that we consume today is significantly different from the wheat consumed by our ancestors. However, these methods allow only for the selective enhancement of characteristics that already exist within a species or compatible species. In recent years transgenic technology, commonly (if not entirely accurately) known as 'genetic engineering', has been developed. This allows for the introduction of genetic material from unrelated species, which would not be possible using conventional methods.

While advocates maintain that there is the potential for biotechnology to have a positive impact on the nutritional properties of transgenic foods and to allow for their cultivation in areas where farming is difficult, it has been argued that most transgenic foods have so far produced greater benefits for producers than consumers. Currently, only six countries (Argentina, Brazil, Canada, China, South Africa and the USA), four crops (corn, canola, cotton and soy) and two traits (herbicide tolerance and insect resistance) represent 99 per cent of the transgenic crops planted worldwide (FAO 2004): 'The so-called "orphan crops" such as cowpea, millet, sorghum and teff that are critical for the food supply and livelihoods of the world's poorest people' and 'traits of interest to the poor; drought and salinity tolerance, disease resistance, or enhanced nutrition' are receiving little attention (FAO 2004). The prospect that transgenic crops could be used for mass medication and vaccination programs also raises concern in some circles.

The long-term safety implications of genetic engineering, a self-regulated industry, are being hotly debated by activists and the public alike. Some of the issues under discussion focus on:

- the consequences of introducing into the food chain questionable genetic material that may produce unpredictable results
- the introduction of lectins, causing immunological effects such as allergic reactions
- the use of bacteria and viruses to introduce foreign material into cells
- the use and potential spread of antibiotic-resistant genes
- the greater use of pesticides and herbicides with transgenic crops
- the contamination of non-transgenic crops with modified genes
- the use of terminator genes and prevention of seed-saving.

Consequently many communities are divided as to whether transgenic foods should be allowed in their country.

Currently, six genetically modified (GM) foods have been approved for sale in Australia and New Zealand: all are derived from soybeans, sugar beet, corn, cottonseed oil, canola and potatoes. In Australia, to enable consumer choice, food producers are required to label foods that contain a GM-derived component or a GM protein introduced through genetic engineering; however, the genetic material that has been used is not specified. The introduction of these transgenic foods has been criticised, with claims that there is insufficient evidence of safety and that safety test technology is inadequate to assess potential harms (Pusztai 2001). It has also been suggested that a precautionary principle should be applied and that further research needs to be conducted on the possible health risks of transgenic foods before they are introduced (BMA 1999). In reality, the ultimate benefits and detriments of genetic engineering are unlikely to be known for several generations.

ANTIBIOTIC RESISTANCE

Approximately one-third of the antibiotics used in Australia are for human use. Two-thirds are used in intensive animal production, of which the majority is mixed into stock-feed to act as a growth promoter (JETACAR 1999). Furthermore, antibiotic resistance genes are sometimes added as marker genes to GM food. This has led to the fear that widespread antibiotic-resistant bacteria have emerged that can cause disease in humans and animals that will be difficult to treat. The British Medical Association has warned that antibiotic resistance is 'one of the major public health threats that will be faced in the 21st century' (BMA 1999), while the World Health Organization has called for a reduction in their use in agriculture (WHO 2001).

FOOD ADDITIVES AND IRRADIATION

Additives are listed as either numbers, known as additive codes, or by name; 'de-coders' are readily available in many bookstores. Up-to-date lists of the food additives used in

Australian and New Zealand food products are freely available from FSANZ (2009). Additives include preservatives, artificial sweeteners, colourings and flavourings, monosodium glutamate, hydrogenated fats and phosphoric acid. Artificial colourings and preservatives in food and drink are thought to contribute to hyperactivity in some preschool children; although many still contest this issue, a recent study in the UK found that the proportion of hyperactive children halved when additives were removed from their diets (Bateman et al 2004).

A further concern is the long-term safety of consuming irradiated foods. Currently irradiation is used for the purpose of food preservation, to control microbes and to protect against critical quarantine pests. Irradiated food is exposed to gamma rays from a radioactive source, which kill insects, eggs, larvae and pathogenic microorganisms. This is an expensive procedure and thus is not extensively used in Australia at present. Currently the *Food Standards Code* in Australia allows for the irradiation of spices, herbs and herbal infusions, and tropical fruits (breadfruit, carambola, custard apple, lychee, longan, mango, mangosteen, papaya and rambutan) as a disinfestation measure for pests such as the fruit fly (FSANZ 2003b).

PROCESSING AND PREPARATION

While production and preservation methods may affect food quality, processing techniques may also significantly affect the therapeutic value of a food, and both benefits and detrimental effects are possible. For example, as both fibre and other nutrients are concentrated in the outer part of the grain, significant losses of not only fibre but also of B vitamins, fat-soluble vitamins and other nutrients occur when grain is refined (Jamison 2006). Similarly, food preparation methods can significantly affect a food's therapeutic qualities. Consider the potentially different nutritional and energetic effects of the same food consumed raw, juiced, steamed, boiled, fried, barbecued or microwaved. The microwaving of broccoli, for instance, has been found to destroy 97% of the flavonoids; conventional boiling destroys 66% and high-pressure boiling causes considerable leaching into the cooking water, whereas steaming produces minimal loss (Vallejo et al 2003).

Cooking does not always have detrimental effects and can sometimes increase the bioavailability of bioactive compounds; for example, the lycopene in tomatoes is more bioavailable when tomatoes are cooked in oil. The concentration of phenolic compounds in a food may also be increased by thermal processing, resulting in a significant increase in overall antioxidant status, despite some loss of heat-sensitive antioxidant nutrients such as vitamin C (Jamison 2006).

Food combination is another factor that influences the therapeutic value of a meal; for instance, consuming red meat with leafy greens and a citrus salad dressing synergistically improves iron absorption. The consumption of antioxidants in the diet, such as the tocopherols, coenzyme Q10, carotenoids, vitamin A, ascorbic acid, reduced glutathione, selenomethionine, flavonoids and other polyphenolic compounds, together with spices and synthetic antioxidants added to food, counteract the effects of pro-oxidants found in food and the environment. Applying this concept, it could be suggested that foods containing high levels of pro-oxidants (e.g. meat) should be served with plenty of antioxidant-containing vegetables, together with sauces, juices, fruits and teas high in antioxidants (Surai et al 2004). This is supported by a study of 2814 male smokers who participated in the Belgian Interuniversity Research on Nutrition and Health study. This found that men with the highest oxidative balance score had a higher relative risk of all-cause mortality (RR = 1.44, 95% confidence interval [CI]: 1.13, 1.82) and of total cancer mortality (RR = 1.62, 95% CI: 1.07, 2.45), compared with men in the lowest-score group (Van Hoydonck et al 2002).

Glycaemic index™

The glycaemic index™ (GI) ranks carbohydrates on their immediate effects on blood glucose levels. Carbohydrate-containing foods that cause a rapid rise in blood glucose are said to have a high GI (> 70), whereas those that cause a slow, steady rise in blood glucose, a more ideal situation, have a low GI (< 55). As insulin is released in response to circulating glucose levels, foods with a high GI will cause a rapid rise in insulin levels. In the presence of chronically elevated levels of circulating glucose and insulin, cells begin to shut down receptor sites, resulting in insulin resistance. Foods that have a low GI rating cause a much slower rise in blood glucose levels and therefore less insulin is secreted in response.

Observational studies indicate that a low-GI diet reduces elevated low-density lipoprotein (LDL) and triglyceride levels, raises

high-density lipoprotein (HDL) levels (Dushay & Abrahamson 2005), and improves fasting glucose and glycated protein values (Anderson et al 2004).

As some foods have a low GI because of their fat content, the GI rating should not be used in isolation, but form part of a sensible approach that limits the amount of saturated and *trans*-fatty acids in the diet. Additionally, other foods that have a high GI, such as potatoes, may also contain substances such as lipoic acid, which is beneficial for the prevention of the long-term complications of diabetes. As such, it is more important to consider the GI or glycaemic load (GL) of the *entire* meal than to eliminate all foods that have a high GI. The GL is calculated by multiplying the number of grams of carbohydrate in a serving of food by the GI value, and is expressed as a percentage: GL = GI (%) × grams of carbohydrate per serving.

Social, cultural and environmental aspects

In addition to being influenced by physicochemical properties, the therapeutic qualities of food may further be affected by a person's psychological state and/or intention while preparing and eating food, as well as by the social, cultural, economic, ethical, religious and environmental impact of the food. It has been said that 'eating is essentially an act of communion with the living forces of nature' (Robbins 1992). Indeed, most cultures and traditions have developed mealtime rituals that acknowledge the source of their food and attempt to align mind and body with the greater forces of nature. Food also features prominently in many spiritual traditions and practices. Thus, the idea of saying grace before meals and then eating 'gracefully' and mindfully, without rushing, may make significant contributions to psychological and spiritual health.

Food and health are both multidimensional and interrelated. Food choices not only influence physiological functioning, but have much broader social, economic, ethical and environmental ramifications, which may in turn affect personal health and wellbeing. Some of these aspects are becoming acknowledged in wider food-related social movements, such as the Fair Trade Federation (see www.fairtradefederation.org), International Slow Food Movement (see www.slowfood.com) and Food Miles (see Sustainable Agriculture–Food and Environment Alliance (SAFE), (see www.sustainweb.org).

Food is not just a means of providing nutrition and sustaining health, it is also a global industry that affects everyone. In the new global economy, there is a fear that the production, trade and retailing of most goods and services are being increasingly concentrated under the control of a small number of corporations that have enormous influence. It is questionable whether all corporations take sufficiently seriously the responsibility of providing quality foods while protecting workers and their environment, and whether free-trade agreements do any more than just offer global protection for a company's intellectual and property rights. For example, global trade in coffee and cocoa has led to social disruption, environmental damage and the mistreatment of workers, including children, who earn meagre wages while corporations make huge profits (Cavanagh 2002).

To counter this trend, the Fair Trade Federation (www.fairtradefederation.org) sets standards for commodities, such as coffee, tea, sugar, cocoa and fruits, that will support living wages and safe, healthy conditions for workers in the developing world. Fair Trade standards stipulate that traders must pay a price to cover the costs of sustainable production and living, and the organisation attempts to support food-producing communities by paying a premium that producers can invest in development, making partial advance payments when requested by producers and signing contracts that allow for long-term planning and sustainable production practices.

The environmental, economic, social and health consequences of the global trade in food are not only influenced by how food is produced but also by its transportation. Nutrients have their best chance to develop under certain climatic conditions; this means that foods grown and harvested seasonally have an advantage and are also more appropriate for eating at those times of year. The ability to transport food around the world allows seasonal food to be eaten year round and creates an enormous economic, social and environmental burden. The environmental and social implications of the rapid escalation in 'food miles', which is the distance that food travels before being consumed, has been reviewed by SAFE, which also considers the effects of food on behaviour and mental health.

The interests of the food industry and agribusiness are not always aligned with the interests and needs of consumers; for example, the

widespread availability of fast foods and their enormous popularity threatens gastronomic traditions, traditional cultivation and processing techniques, while standardising taste. The Slow Food Movement is an international movement that originated in Italy; it attempts to address these concerns by:

- promoting regional food and wine cultures, while defending food and agricultural biodiversity worldwide
- opposing the standardisation of taste
- defending the need for consumer information
- protecting cultural identities tied to food and gastronomic traditions
- safeguarding traditional foods.

Unfortunately the exploitation of natural and human resources comes at a cost. For too long, the external costs of agribusiness have been delayed, resulting in the availability of artificially 'cheap' but nutritionally depleted food. The food production industry is now faced with new challenges: the results of years of hyperintensive farming practices (soil erosion, contamination of water sources, superbugs), the effects of climate change, water shortages; rising oil prices (required for transportation, food processing and the production of pesticides and fertilisers); the diversion of food grain for ethanol production; and the loss of arable land to urbanisation. All these challenges must be met with nutritionally, socially and environmentally responsible solutions.

PRINCIPLES OF USING FOOD AS MEDICINE

It is often said that 'you are what you eat'; however, it may be more accurate to say that 'you are what you absorb from what you eat'. Food choices can exert a profound positive or negative influence on individual health, as well as on the health of communities and the environment. While the research community establishes the mechanisms by which foods exert their biological effects, there are some general recommendations that can enhance the positive impact of food, summarised by the mnemonic SLOW: consume food that is

- **S** **S**easonal
- **L** **L**ocally produced with lots of colour and variety
- **O** **O**rganic
- **W** **W**hole, fresh and with minimal processing.

THERAPEUTIC POTENTIAL OF COMMON FOODS

When consuming or prescribing functional foods, consideration should be given not only to the selection of foods for their potential therapeutic benefits, but also to the quality of the food consumed (as discussed earlier), and to the digestive function and health status of the individual. It should be noted that no single food should be eaten to the exclusion of others, and the inclusion of functional foods should form part of an otherwise balanced diet. Several examples of foods that may be incorporated into the diet for physiological benefit are discussed here, but a range of foods are covered in greater depth in the monographs.

Blueberries (and other berries)

A growing body of research suggests that the dietary intake of berry fruits has a 'positive and profound impact on human health, performance, and disease' (Seeram 2008). Berry cousins blueberry (*Vaccinium corymbosum*), cranberry (*Vaccinium macrocarpon*) and bilberry (*Vaccinium myrtillus*) have demonstrated significant benefits in the past, and there has recently been increased interest in other berry-type fruits such as pomegranate (*Punica granatum*), goji berry (*Lycium barbarum*), mangosteen (*Garcinia mangostana*) and the Brazilian acai berry (*Euterpe oleraceae*).

Blueberries, native to East Asia and the USA (Natoli 2005), are readily available fresh during the warmer months and frozen or juiced year round. They were traditionally used by the North American Indians for the treatment of diarrhoea and labour pains (Pratt & Matthews 2004a) and are an excellent source of antioxidant nutrients and phenolic compounds that work synergistically within the body (including vitamin C, beta-carotene, flavonoids, anthocyanins and resveratrol) (Natoli 2005, Pratt & Matthews 2004a). The anthocyanins are powerful antioxidant and anti-inflammatory agents, responsible for the deep blue-purple colour of blueberries; the deeper the colour, the greater the anthocyanin content (Pratt & Matthews 2004a).

The majority of studies to date rely on in vitro, animal and epidemiological evidence. Blueberry and its cousins appear to 'limit the development and severity of certain cancers and vascular diseases including atherosclerosis, ischemic stroke, and neurodegenerative

diseases of aging' (Neto 2007). The antioxidant and anti-inflammatory effects of blueberries have been associated with an improvement in age-related cognitive and motor deficits, spatial working memory tasks and neurodegenerative disorders such as Alzheimer's dementia (Bickford et al 1999, 2000, de Rivera et al 2005, Galli et al 2006, Lau et al 2005, Ramirez et al 2005, Wang et al 2005, Williams 2008) and reduced risk of cardiovascular disease (Kalea et al 2006, Youdim et al 2002). Recent animal studies suggest improved growth capacity in neural transplants (Willis 2008); a reduction in total and LDL cholesterol (Kalt 2008) and prevention of bone loss (Devareddy et al 2008). Anticarcinogenic properties have also been demonstrated in prostate cell lines, and blueberry extracts have been shown to suppress tumour growth, protect the integrity of DNA (Natoli 2005), reduce angiogenesis (Atalay et al 2003), inhibit the proliferation of androgen-dependent prostate cancer cells (Schmidt et al 2006), prevent oestrogen-induced mammary tumors (Aiyer 2008), and reduce the risk of metastasis (Matchett et al 2006). Blueberry may also act synergistically with cranberry to inhibit *Helicobacter pylori* (Vattem et al 2005) and human clinical trials have demonstrated improved exercise capacity in hot environments (McAnulty et al 2004).

Choose dark blue-purple berries that move freely in the container. Damaged berries will inhibit movement and be prone to mould and should be discarded before storage. Organic fruit is preferable because it has higher concentrations of malic acid, phenolics, anthocyanins, and overall higher antioxidant activity (Wang et al 2008). Although the vitamin C content degrades rapidly during heating and storage, many of the phenolic compounds may actually become more bioavailable, improving the overall antioxidant capacity (Wehrmeister et al 2005). Frozen berries maintain the phenolic compounds and provide an excellent source for year-round availability (Srivastava 2007). As blueberries contain salicylates, those with a known sensitivity should be cautious about consuming them (Natoli 2005).

Broccoli (and cruciferous vegetables)

Broccoli, originally grown in the Mediterranean region and cultivated by the ancient Romans, belongs to the cruciferous family of vegetables (Brassicaceae), so called because of the cross-shaped structure of the leaves and flowers (Pratt & Matthews 2004b). The family also includes cauliflower, Brussels sprouts, cabbage and kale, which have also demonstrated significant therapeutic potential. Broccoli is low in kilojoules and an excellent source of fibre; calcium; folate; vitamins C, E and K; coenzyme Q10; iron; sulforophane; indoles; phenolic compounds (quercetin, kaempferol, hydroxycinnamoyl acids); and the carotenoids beta-carotene, cryptozanthin, lutein and zeaxanthin (Damon et al 2005, Lucarini et al 1999, Podsedek 2005, Pratt & Matthews 2004b). The antioxidant nutrients in broccoli work in synergy to reduce reactive oxygen species and recycle each other (Podsedek 2005); however, significant variations occur in nutrient levels because of differences in variety, maturity at harvest, soil quality, sunlight exposure, growing environment, processing and storage conditions (Jeffery et al 2003, Gliszczynska-Swiglo et al 2005, Podsedek 2005).

Numerous epidemiological studies have established an inverse association between the consumption of cruciferous vegetables and the incidence of cancer (especially lung, colon, stomach, rectal, bladder and premenopausal breast cancers) (Brennan et al 2005, Cortizo & Vitetta 2004, Kim et al 2003, Pratt & Matthews 2004b, Tang 2008). When broccoli is crushed or chewed, glucoraphanin (a glucosinolate) is converted by the action of myrosinase into isothiocyanates, the most studied of which is the powerful anticarcinogenic compound known as sulforophane (Matusheski et al 2004). Young broccoli shoots are the best source of the chemoprotective glucosinolates, containing 20–50-fold the content of the more mature vegetable (Cortizo & Vitetta 2004). In animal and in vitro studies, isothiocyanates have demonstrated chemoprotective activity against different types of tumours, enhancing detoxification of carcinogens, blocking the initiation of chemically induced carcinogens, inducing apoptosis and modulating cell-cycle progression in highly proliferative cancer cells (Cortizo & Vitetta 2004, Fimognari et al 2005, Gills et al 2005, Hintze et al 2003, Rose et al 2005, Jadhav et al 2007). Indoles, such as indole-3-carbinol, have also been shown to exert chemopreventive effects in liver, colon and mammary tissue (Kang et al 2001) and to arrest human tumour cells in the G1 phase of the cell cycle (Matsuzaki et al 2004); they may also block oestrogen receptors in breast cancer cells (Pratt & Matthews 2004b).

Although the anticarcinogenic, antioxidant and anti-inflammatory benefits of broccoli compounds help to explain their therapeutic

effects, the exact mechanisms are still unclear and contradictory evidence exists for a role in inhibiting phase I and inducing phase II enzymes (Cortizo & Vitetta 2004, Knize et al 2002, Myzak & Dashwood 2005, Perocco et al 2006, Steinkellner et al 2001, Vang et al 2001). Furthermore, several authors warn of potential risks resulting from uncontrolled use of isolated compounds from broccoli (Fimognari et al 2005, Perocco et al 2006, Wiseman 2005); therefore, consumption of the plant itself is currently more advisable than isolated extracts.

Human clinical trials demonstrated a reduction in LDL-cholesterol in 77 hypercholesterolaemic patients (Takai et al 2003). Additional benefits for cardiovascular health are suggested by in vitro evidence indicating that broccoli compounds may bind to bile acids (Kahlon et al 2007) and have an ACE inhibitor activity (Lee et al 2005). Broccoli contains high amounts of selenium and glucosinolates, which can exert a cardioprotective effect (Mukherjee et al 2008). Because of its known nutrient content, broccoli may support the immune system; it may also reduce the risk of cataracts, osteoporosis and neural tube birth defects (Podsedek 2005, Pratt & Matthews 2004b).

Choose young plants or shoots with a dark-green–purplish colour. As broccoli is prone to infestation and has a large surface area, agricultural chemical residue can be an issue, and ideally organic broccoli should be purchased and inspected for pests. Broccoli will store at 5°C (non-packaged) for 1–3 weeks without significant nutrient loss (Favell 1998, Leja et al 2001), although processing methods may affect nutrient quality (Podsedek 2005). Although cooking degrades the vitamin C and isothiocyanate content, the carotenoids may become more bioavailable, increasing the potential overall antioxidant activity (Bernhardt & Schlich 2005, Pratt & Matthews 2004b, Turkmen et al 2005, Tang et al 2008). Light steaming (approximately 1 minute) of raw broccoli is likely to maintain the best nutritional profile. Despite concerns that goitrogenic compounds in broccoli may increase the risk of thyroid cancer, a meta-analysis found no correlation (Cortizo & Vitetta 2004); nevertheless broccoli should not be consumed in excess by those with known thyroid disease. A serving size of half to 1 cup per day is associated with a significant reduction in cancer risk (Pratt & Matthews 2004b).

Single-cell foods

Microalgae are both single cells and whole plants that are at the bottom of the food chain and are the most productive organisms on the planet, using light approximately three times more efficiently than higher plants (Pirt 1980). Gram for gram microalgae may also be the most nutrient-dense food on earth (Passwater & Solomon 1997), with minimal indigestible structures in contrast to higher plants or animals, in which less than half their dry weight is typically nutritionally useful (Bruno 2001).

Microalgae, which include *Spirulina* and *Chlorella* species, and the 'red-orange' algae *Dunaliella salina*, contain a range of macro- and micronutrients, such as chlorophyll, carotenoids, phytonutrients, amino acids, polysaccharides, essential fatty acids, carbohydrates and vitamins, and bioavailable minerals (Cases et al 1999, Chamorro et al 2002, Kay 1991). They may also promote the growth of lactic acid bacteria in the gastrointestinal tract (Parada et al 1998).

These organisms can be considered to be a mix of food, supplement and medicine. As single-cell plants, they represent 'whole' foods; however, they are often marketed in capsules and can be taken as supplements and/or medicines. In contrast to the reductionist approach to nutrition, which leads to supplementation with only a few specific nutrients, microalgae provide a complex mix of nutrients developed over millions of years of evolution. Although accumulating research suggests that microalgae have many health benefits, further research is required to determine their clinical applications.

The cyanobacteria *Spirulina* spp (usually *Spirulina platensis* or *S. maxima*) contains pigments, called phycobilins or phycobiliproteins (including phycocyanin and allophycocyanin), that are similar in structure to bile pigments (Pinero Estrada et al 2001). *Spirulina* spp are said to possess antiviral, hypocholesterolaemic, antioxidant, anti-inflammatory, hepatoprotective, anti-allergic and immunomodulatory activities and have been used to treat certain allergies, anaemia, cancer, viruses, cardiovascular diseases, hyperlipidaemia, immune deficiency, and inflammatory processes (Chamorro et al 2002, Hirahashi et al 2002).

In vitro studies of spirulina suggest antiviral and antiretroviral activity by inhibiting the penetration of viruses into host cells and also the replication of several enveloped viruses, including human cytomegalovirus,

measles virus, mumps virus, influenza A virus and HIV-1 (Ayehunie et al 1998, Hayashi & Hayashi 1996, Hernandez-Corona et al 2002).

Spirulina extracts enhance macrophage activity (Quereshi & Ali 1996), and humoral and cell-mediated immune functions in animal studies (Quereshi et al 1996), and may also act as anticlastogenic (Ruiz Flores et al 2003) and antitumour agents (Li et al 2005). They inhibit mast-cell-mediated immediate-type allergic reactions in vivo and in vitro (Kim et al 1998), possibly by inhibiting mast-cell degranulation.

Animal studies have demonstrated that spirulina reduces vascular reactivity (Mascher et al 2006), possesses hypocholesterolaemic (Devi & Venkataraman 1983), anti-atherogenic (Kaji et al 2002, 2004) and antioxidant activity (Pinero Estrada et al 2001), reduces chromosomal damage and lipid peroxidation, and increases liver enzymes and non-enzymatic antioxidants (Premkumar et al 2004). The hepatoprotective effects are likely caused by the antioxidant activity. Although some green foods are touted as being a good source of vitamin B_{12} for vegetarians, and this is true of chlorella, the B_{12} in spirulina appears to be in a largely inactive form (Watanabe et al 2002). Spirulina extract is an excellent selenium carrier and therefore enriched sources can provide a highly bioavailable source of selenium (Cases et al 1999).

Chlorella (usually *Chlorella vulgaris* or *C. pyrenoidosa*) has been promoted as an anticarcinogenic, immunomodulatory, hypolipidaemic and gastric mucosa-protective agent. As with other green foods, the antitumour activity is thought to be mediated by an immunopotentiation mechanism (Noda et al 1996), and extracts of chlorella have demonstrated antitumour activity against both spontaneous and experimentally induced metastasis in the lymphoid organs of mice (Tanaka et al 1998). Based on animal studies, chlorella may also ameliorate some of the side effects of 5-fluorouracil chemotherapy treatment (Konishi et al 1996).

Chlorella vulgaris extract enhances resistance to *Listeria monocytogenes* through augmentation of Th1 responses, producing gamma-interferon (Hasegawa et al 1999). It may be useful for the prevention of allergic diseases (Kralovec et al 2005), especially in those people with a predominantly Th2 response (Hasegawa et al 1999).

In some animal experiments, chlorella appears to possess hypolipidaemic (Sano et al 1988) and anti-atherogenic effects (Sano & Tanaka 1987). It may prevent dyslipidaemia in animals chronically fed a high-fat diet by preventing intestinal absorption of redundant lipids and thus reducing triglyceride, and total and LDL-cholesterol levels (Cherng & Shih 2005). In addition, inhibition of advanced glycation end products in vitro suggests a possible role for reducing atherogenesis, diabetic microangiopathy and Alzheimer's dementia (Yamagishi et al 2005).

Chlorella may also exhibit hypoglycaemic activity (Cherng & Shih 2006), improve insulin sensitivity (Jong-Yuh & Mei-Fen 2005) and prevent stress-induced ulcers (Tanaka et al 1997), according to animal studies.

Although it has been suggested that a diet high in spirulina may be a risk for kidney stones, this may be the case only with a high or excessive intake of oxalic acid (e.g. beetroot leaves or rhubarb) (Farooq et al 2005), as the antioxidant activity of phycocyanin appears to aid in the prevention of calcium oxalate stones (Farooq et al 2004). Occasional gastrointestinal symptoms and allergic reactions have been reported for spirulina and chlorella, and those taking warfarin should avoid chlorella, which can be high in vitamin K.

Doses of spirulina range from 250 mg to 5 g daily (PDR Health 2006). High doses of chlorella (10 g/day) have been used successfully in clinical trials for fibromyalgia (Holdcraft et al 2003, Merchant & Andre 2001), but the standard dose is usually 200–500 mg/day (PDR Health 2006).

Dunaliella salina is a soft-celled microalga found in many coastal waters and saltwater lakes (see the monograph on Dunaliella). It is one of the most salt-tolerant life forms known, and is adapted to extremely high UV radiation. To cope with these extreme environments, *Dunaliella* produces very high levels of antioxidant molecules. On a per-gram basis, *Dunaliella* has more than twice the chlorophyll, five times the mineral content and more than 6000 times the carotenoid antioxidants content of spirulina (Table 5.2), with the carotenoids giving it an orange rather than a green colour. Furthermore, *Dunaliella*'s soft-cell membrane makes it easily digestible, compared with other microalgae that have hard cell walls (Ben-Amotz & Avron 1983). To date, most of the clinical research on *Dunaliella* has been on beta-carotene-containing extracts rather than on the whole organism, but recent advances in production technology have allowed the whole, dried *Dunaliella* biomass with its full range of nutrients and minerals to become commercially available (Table 5.3) (Tracton & Bobrov 2005), and more studies

TABLE 5.2 Nutrient Content of *Dunaliella* Compared with *Spirulina* and Carrots (per 100 g)

Nutrient	*Dunaliella*	*Spirulina*	*Carrots*
Protein	7.4 g	57 g	1 g
Fat (total)	7 g	8 g	0
Carbohydrates	29.7 g	24 g	10 g
Energy	893 kJ	1214 kJ	180 kJ
Fibre	0.4 g	4 g	3 g
Chlorophyll	2210 mg	1000 mg	NA
Minerals	49 g	6.2 g	1 g
Beta-carotene	2100 mg	0.34 mg	8.3 mg
Alpha-carotene	53 mg	0.0 mg	3.5 mg
Lutein/zeaxanthin	97.6 mg	0.0 mg	0.26 mg
Cryptoxanthin	46.5 mg	0.0 mg	0.1 mg

Source: Data obtained from: US Department of Agriculture, National nutrient database for standard references, release 18, 2005 (available online: www.nal.usda.gov); National Measurement Institute (Australia) (available online: www.measurement.gov.au); Craft Technologies Inc. (USA) (available online: www.crafttechnologies.com).

TABLE 5.3 Comparison of the Nutrient and Trace Minerals in 'Super' Foods (mg/100 g)

Food	Ca	Mg	Na	K	Cu	Zn	Fe
Dunaliella salina	178	5394	7513	5	0.4	4	23.5
Spirulina	547	330	> 999	5	1.1	2	50.5
Chlorella	201	211	106	5	0.1	1	214
Kelp powder	1443	796	> 999	7	0.2	3	27
Wheat grass	937	83	315	6	0.4	2	13.7
Green barley	384	186	818	6	0.6	2	8.4

Food	Mn	Cr	Se	B	Co	Mo	S	Li	Rb
Dunaliella salina	1.8	0.2	1.02	25.4	0.022	0.041	3105	0.9	0.66
Spirulina	2.6	0.53	0.03	0.25	0.13	0.11	< 2000	0.093	0.13
Chlorella	4	0.06	0.01	0.03	0.038	0.042	< 2000	0.01	0.066
Kelp powder	3.8	0.23	0.69	11.1	0.045	0.094	2426	0.068	0.85
Wheat grass	5.1	0.09	0.04	0.33	0.005	0.05	< 2000	0.008	1.0
Green barley	3.9	0.11	0.15	1.05	0.004	0.066	< 2000	0.023	0.51

Source: Data obtained from: Trace Elements Inc. (USA) (available online: www.traceelements.com).

are likely to include the whole organism in future.

Medicinal mushrooms (reishi, shiitake)

Mushrooms such as shiitake (*Lentinus edodes*), reishi (*Ganoderma lucidum*), oyster (*Pleurotus ostreatus*) and maitake (*Grifola frondosa*), to name only a few, have also been used as medicinal agents in Asia for thousands of years (Chang 1996, Sliva 2004). More recently the benefits of the common button mushroom (*Agaricus bisporus*), widely cultivated in the West, have also begun to be elucidated (Beelman et al 2004). Although the nutritional and medicinal potential of mushrooms may differ because of variations in species, cultivation techniques, maturity at harvest and other factors, numerous common features arise.

In general, mushrooms contain significant amounts of water (>90%) and, as a result, nutrients measured on the fresh-weight values may appear to be quite low. Nevertheless, they are low in kilojoules and a good source of fibre (including glucans and chitin), amino acids, B vitamins, copper, selenium, potassium, germanium, ergosterol (Beelman et al 2004) and lipids, especially linoleic acid (Yilmaz et al 2005).

The immunostimulatory properties of a variety of polysaccharides found in mushrooms are thought to contribute to their anticancer effects, and other biologically active substances, including triterpenes, cerebrosides and phenols, have been identified and characterised in the medicinal mushrooms in particular (Sliva 2004). Mushrooms may also protect against oxidative damage to DNA (Beelman et al 2004)

Shiitake mushrooms (*Lentinus edodes*) possess immunomodulating, antitumour, hypolipidaemic, antibacterial (Hirasawa et al 1999) and antioxidant properties (Cheung et al 2003), and may help to reduce dental caries, according to in vitro and animal studies (Shouji et al 2000). They have been traditionally used for exhaustion, colds, intestinal parasites, poor circulation and liver problems (PDRHealth 2006).

Lentinan, which is a biologically active beta-glucan in shiitake mushrooms, modulates the immune system (including T-lymphocytes and cytokines); suppresses hepatic expression of cytochrome P1A (Okamoto et al 2004); and has demonstrated antitumour and antimetastatic activity against chemical and viral carcinogens (Mitamura et al 2000, Ng & Yap 2002, Zheng et al 2005). However, clinical trials using shiitake extract in men with prostate cancer were not successful in reducing levels of prostate-specific antigen (White et al 2002), although other compounds may also contribute to the antitumour effects (Sia & Candlish 1999). Lentinan is antifungal and may also exert an inhibitory effect on HIV-1 reverse transcriptase and proliferation of leukaemia cells (Ngai & Ng 2003).

Lentinus edodes mycelia inhibit atherosclerotic development in rabbits (van Nevel et al 2003) and contains eritadenine, a hypocholesterolaemic compound that also acts as an immunomodulator and tumour-inhibitor in animal models (Beelman et al 2004, Yamada et al 2002). Extracts from shiitake mushrooms have been shown to elevate plasma insulin and reduce plasma glucose, total cholesterol and triglyceride levels in rats (Yang et al 2002).

Ganoderma lucidum (reishi) has been used in TCM for thousands of years for the treatment of asthma, cough, fatigue, insomnia and weakness, and was popular as a cancer chemotherapy agent in ancient China (Sliva 2003). There is some confusion about the taxonomical classification of reishi mushrooms and, as a result, a variety of different medicinally active compounds with significantly different pharmacological effects may be attributed to different strains, adding confusion to the body of evidence available (Szedlay 2002).

The anticancer activity may be due to direct cytotoxic effects against tumour cells, inhibition of angiogenesis (Lin & Zhang 2004), and the effects of immunomodulatory polysaccharides (Chen et al 2004), which act by stimulating the expression of cytokines (especially IL-1, IL-2 and IFN-gamma) (Wang et al 2002) and modulating humoral and cellular immunity (Lin 2005).

Agaricus bisporus may modulate aromatase activity and function, resulting in chemoprevention of the deleterious effects of in situ oestrogen in breast cancer (Grube et al 2001). It has also been suggested as a potential agent for preventing scarring and promoting healthy wound-healing (Batterbury et al 2002, Kent et al 2003). The browns strains (Swiss browns, portabellas) harvested when fully mature, with open caps, appear to be the most useful (Beelman et al 2004).

High doses of shiitake mushrooms may cause rash, diarrhoea and bloating, and consumption of 4 g shiitake powder has been associated with marked eosinophilia (Levy et al 1998). Reishi mushrooms should not be consumed daily in the long term (> 3–6 months), as they may cause dizziness, dry mouth, nose bleeds and gastrointestinal upset, and may potentially produce additive effects with anticoagulant medications (PDRHealth 2006).

Agaricus bisporus contains agaratine, a hydrazine compound with suspected carcinogenic potential (Hashida et al 1990). To date, animal studies have demonstrated different outcomes between species and no conclusive evidence exists for a cause–effect relationship between mushroom intake and cancer prevalence in humans. In addition, the potential anticarcinogenic properties of other compounds in mushrooms may provide protection (Beelman et al 2004). Although there are concerns about heavy metal toxicity in wild *Agaricus* mushrooms, levels of mercury and cadmium in

commercially cultivated mushrooms have been found to be very low (Kalac & Svoboda 2000, Vetter & Berta 2005).

Agaricus mushrooms (including Swiss browns and portabellas) and shiitake mushrooms are readily available fresh or dried, and dried reishi mushrooms can sometimes be found in Asian grocery stores. Dried mushrooms can be reconstituted in warm water for use in cooking. Cooking mushrooms may increase free polyphenolic compounds (Choi et al 2006) but can make them tough and result in losses of manganese, zinc and iron (Coskuner & Ozdemir 1997).

FUTURE DIRECTIONS

Despite advancements in medicine and pharmaceutical drug development, dietary choices remain the cornerstone of preventative medicine and enhance the health of individuals and societies. Emerging research indicates exceptional potential for the benefits of using 'food as medicine'. Recognising the inherent therapeutic value of foods or their potential to induce harmful health consequences means that we can tailor the diet to produce better health outcomes.

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CHAPTER 6
INTRODUCTION TO THE PRACTICE OF INTEGRATIVE MEDICINE

Throughout history, every civilisation and culture has developed its own form of medicine. The rise of modern technology and scientific enquiry has added new therapeutic techniques, products and services to the range of traditional therapies. Thus, within today's pluralistic, multicultural and increasingly globalised societies, the wisdom and therapeutic interventions of many different traditions are becoming available. While it is impossible for any practitioner to have access to, or even know something about, the many hundreds of therapeutic interventions available, it is possible to incorporate some of the key principles into today's conventional healthcare practice. This leads to the practice of integrative medicine (IM), which attempts to define and embrace these principles.

The practice of IM is more than simply an expansion of conventional medical practice to include 'complementary therapies' such as mind–body techniques, acupuncture, herbs, nutrients and body work (for example, massage and manipulation). It involves:

- a focus on the whole person: the interplay between the physical, emotional, spiritual and psychological states
- highly individualised treatment plans that are tailored to meet the needs of the person
- development of a therapeutic partnership between the patient and practitioner as a fundamental part of the healing process
- a primary focus on prevention, health enhancement and addressing predisposing, exacerbating and sustaining causes of disease
- integration of the best available, evidence-based, safe and ethical therapies from different traditions.

As such, IM implements principles that form the basis for clinical decision making and improving patient outcomes, by providing each patient with effective and compassionate care and healing on many levels. IM is increasingly being acknowledged as 'best practice'; however, it requires some fundamental shifts in the way in which healthcare is delivered and has not yet become widely implemented (Cohen 2005a). For example, the use of complementary medicines is an integral part of IM practice, yet this use raises many issues for medical practitioners, particularly those who have not received training in how to use them. Some of the questions are:

- What can be reasonably expected by providing integrative care?
- What are the safety issues?
- Which therapies are cost-effective?
- What advice should be given to patients in the absence of definitive evidence?
- Which therapies or products are useful for which conditions and which patients?
- Where can high-quality complementary and alternative medicine (CAM) products be obtained?
- Which specially trained practitioners should patients be referred to, and when, how and for what reasons should referrals be made?
- Where can reliable information about CAM be found, and what pathways are there for further study?

These are core issues in any healthcare practice and are not specific to the use of complementary medicines or even to the practice of IM. The practice of IM, however, poses additional challenges to medical practitioners, both professionally and personally. It requires being prepared to learn about new

and different treatment systems, traditions and ways of thinking, and recognising the advantages and limitations of both complementary and conventional medicine and the potential benefits of combining them. It also requires adopting a collaborative approach with patients and a variety of different healthcare professionals, while allowing old beliefs to be challenged and re-evaluated. Furthermore, the practice of IM challenges medical practitioners to develop their intuition, empathy and compassion, address their own health and personal growth, and become role models for their patients and the wider community. From a practical perspective, developing IM takes extra time. Time is needed to keep up to date with the changing evidence base, as well as to establish a holistic understanding of patients and then apply the principles of IM to address their needs.

HOLISM AND THE INDIVIDUAL

In their professional training, medical practitioners study the biological, psychological and social aspects of health, as well as the signs, symptoms and pathophysiology of specific illnesses, to achieve an understanding of health and disease in a clinical context. This knowledge base must be updated and modified with new knowledge provided by new scientific evidence and cumulative clinical experience. Although consideration of the best available evidence is an important dimension of clinical practice, scientific data are often based on a group of observations that give statistical information about research populations, but which may not provide definitive information about what will happen to any individual patient in certain circumstances.

Each human being is unique and presents in a specific clinical context, in which the outcome will be determined by personal attributes such as attitudes, education and understanding, as well as by genetics, physiology, past experiences, socioeconomic and cultural circumstances, available resources and lifestyle. Accounting for individual differences is an essential aspect of the art of medicine and is a cornerstone of many ancient systems of medicine.

Chinese medicine, Ayurvedic medicine and Western herbal medicine all have sophisticated systems of categorising people according to their different physiological and psychological characteristics in order to guide treatment selection. In comparison, modern Western medicine has been slow to accept and use this individualistic approach, preferring to standardise treatment approaches through clinical guidelines and protocols. The fields of pharmacogenomics and nutrigenomics, which have emerged out of the Human Genome Project, are beginning to provide a scientific rationale for individualising treatments. These new fields emphasise two factors: individualised response to medicines and nutrients, and the roles of dietary and genetic interactions in patient health.

The practice of IM combines both ancient and modern knowledge, and takes a holistic perspective that recognises that health involves physical, psychological, social, spiritual and environmental dimensions. This is in line with increasing patient expectations to have the accompanying social and psychological aspects of their illness addressed, not just their presenting symptoms (Jonas 2001). Thus the practice of IM requires careful history taking and physical examination, which may include obtaining information from different philosophical perspectives, together with astute and appropriate investigations and obtaining other information from relatives or carers.

Accounting for individual factors takes considerable time, yet this time is well spent because there is mounting evidence to suggest a direct relationship between consultation length and the quality of care. Longer consultations are likely to result in better health outcomes and better handling of psychosocial problems, fewer prescriptions, more lifestyle advice and lower costs, less litigation and more patient and doctor satisfaction (Cohen et al 2002).

THERAPEUTIC RELATIONSHIPS

Although amassing personal information about a patient is a time-consuming process, it is an extremely valuable one, not only for the information gleaned but also because it facilitates the development of rapport, respect and trust, thus laying the foundation for the therapeutic relationship. The development of close and meaningful relationships with people in a clinical context is one of the great challenges of holistic or integrative practice. It is also one of the most powerful therapeutic tools clinicians have and may be more important than any specific treatment modality.

The therapeutic relationship is a profound and sacred one, acknowledged since ancient

times and codified in the Hippocratic oath, which has specific phrases that dictate the principle of doctor–patient confidentiality, as well as the responsibility of clinicians to exercise a duty of care. A therapeutic relationship is established with the specific intention of healing, and the act of establishing such a relationship, in which intuition and empathy are valued alongside information and evidence, may be therapeutic in itself. Simply articulating one's personal story and expressing traumatic experiences to a sympathetic listener can help people make connections and better understand the causes and implications of their disease, as well as providing much needed psychosocial support.

Healthcare professionals commonly see people at their worst: when they are in pain and/or feeling sick, scared, sleep deprived and fearful of the possible implications of an illness. The constant stream of 'sick people' can make it easy to start differentiating patients by their illnesses; however, thinking of people in terms of their highest level of functioning may be more productive. To this end, some of the most important questions a practitioner can ask are: 'What makes you happy?' or 'What makes you feel alive?' The answers to these questions can provide valuable insight into an individual and form the basis for a more meaningful relationship than the answer to the question: 'What is the problem?'

Developing rapport, trust and a holistic understanding of patients' lives is one of the most important elements in IM, because it places practitioners in a better position to allay their patients' fears, adequately address the issues of most concern, and help to reduce the burden of stress that accompanies virtually all illness. A holistic understanding of a person also enables clinicians to recommend treatments that are more likely to be successfully integrated into a patient's social and cultural environment, thus improving efficacy and compliance. Furthermore, a sound therapeutic relationship provides the camaraderie and sense of therapeutic adventure necessary to underpin a partnership model of health and provides a solid foundation for clinical decision making.

PRACTITIONER WELLBEING

Healthcare professionals experience significant mental, physical and spiritual demands during the course of everyday practice. In addition, personal stress can influence the ability to deliver effective care, establish therapeutic relationships and maintain good health. Over time, exposure to multiple stressors can lead to physical and emotional exhaustion, or burn out, with its accompanying physical and psychological burden (Dunning 2005).

For some practitioners, there is a perceived pressure to symbolise perfect health and be invulnerable to disease. As a result, there is the temptation to avoid indications of ill health in themselves and their colleagues and a failure to see the need for self-care.

The practice of IM compels clinicians to address their own health and lifestyle, explore their emotional life and develop self-care routines to maintain wellbeing and prevent disease. In addition, the therapeutic relationship developed with patients can be nurturing for the practitioner, with rewards that flow in both directions (Cohen 2005b).

In advocating a holistic view of health, the practice of IM can motivate practitioners to become more involved in broader community, public health and global issues, such as social justice, fair trade, environmental preservation, regeneration and sustainability, as well as spiritual, ethical and philosophical debates and pursuits.

INTUITION, BEDSIDE MANNER AND PLACEBO

Medicine is an art informed by science, yet with so much recent attention being given to scientific evidence, it is easy to forget the importance of intuition and clinical experience. A holistic understanding of a patient, together with empathy and compassion for a patient's circumstances, adds important information to any clinical encounter. It is likely that the best and most inspired practice occurs when the practitioner's academic knowledge, clinical experience and intuitive understanding of the individual merge to provide a picture of the clinical situation as a coherent whole, known as the 'Gestalt' approach.

Developing an intimate therapeutic relationship and integrating rational and intuitive knowledge enlists the full capacity of the practitioner. It may also be the best way to tap into patients' unconscious healing processes and elicit the 'placebo response'. The placebo effect is often considered a source of bias and a scientific distraction that research methodology must minimise; however, the placebo response is ubiquitous and cannot be avoided in the clinical setting. All interventions have a

non-specific therapeutic action, in addition to their purported activity, and the best clinicians will always use their 'bedside manner' to harness the 'placebo response' and enhance the therapeutic benefits of any specific intervention. Herbert Benson suggested that the placebo response is based on a good therapeutic relationship, as well as positive beliefs and expectations on the part of the patient and practitioner and furthermore can yield beneficial clinical results and be a powerful adjunct to therapy. Benson, who coined the term 'the relaxation response' in reference to meditation, further suggested that the placebo response should be renamed 'remembered wellness', and that it may be one of medicine's most potent assets because it is safe, inexpensive and accessible to many people (Benson & Friedman 1996).

In addition to the use of rapport, empathy, compassion, trust, confidence and intimacy, an integral part of a good bedside manner is the appropriate and thoughtful use of touch. Touch pulls together psychological and bodily experiences and is important in relationships between people in general, and the therapeutic relationship in particular. It is a basic human need that enhances communication and builds up trust. A simple handshake to acknowledge each other's presence or hand-holding when bad news is delivered can provide important and reassuring support that goes beyond words. The therapeutic power of touch has been recognised and practised throughout history: for example, through the art of massage, which, when provided by trained practitioners, can produce substantial therapeutic effects, enhance a person's sense of wellbeing and promote a sense of calm and peace.

BIAS IN MEDICAL DECISION MAKING

How do people make decisions and how do they choose between different treatment options? Decisions are made using 'heuristics', or general rules of thumb, which reduce the time and effort required. Normally this method yields fairly good results; however, there are times when they lead to systematic biases (Plous 1993). In these situations, assumptions are made and information is neglected, downplayed or overplayed, or based on what is easily recalled. In healthcare, unrecognised bias of this nature can have dire repercussions, affecting a clinician's ability to diagnose and treat effectively and a patient's ability to make good choices.

It is both normal and human to have a range of biases that influence the types of treatments that are considered appropriate, based on the individual's personal, ideological, religious, ethical, cultural, educational and philosophical ideals and experiences. Good clinicians are aware of their personal biases and will openly disclose those that may influence a patient's care. In some cases, this is easier said than done. Stating known or potential bias can be particularly sensitive when the practitioner has strongly held religious beliefs that may limit their practice or determine their attitudes to different therapies, as well as when it comes to declaring commercial interests.

Healing is a human vocation that arises from the desire to do the best for humanity. The patient–practitioner relationship, however, is not only a therapeutic one, it is commonly a commercial one. Healing is a business that sustains the personal lives of individual practitioners and drives the pharmaceutical industry. In 2002 the combined profits for the top 10 drug companies in the Fortune 500 list were greater than those of all the other 490 companies combined (Angell 2004).

One important source of bias that is becoming increasingly recognised concerns the millions of dollars spent by the pharmaceutical industry in a bid to influence doctors' decision making. The seemingly unlimited marketing budgets and provision of gifts, luxuries and educational events has forced the medical profession to attempt to limit these sorts of inducements (Studdert et al 2004). The extent of the industry's influence is vast and has not always been obvious. In her book on the pharmaceutical industry, Marcia Angell, a former editor-in chief of the *New England Journal of Medicine*, states:

> Over the past two decades the pharmaceutical industry has moved very far from its original high purpose of discovering and producing useful new drugs. Now primarily a marketing machine to sell drugs of dubious benefit, this industry uses its wealth and power to co-opt every institution that might stand in its way, including the US Congress, the FDA, academic medical centers, and the medical profession itself.
> *Angell 2004*

Not only are doctors subject to the influence of the pharmaceutical industry, they may also have other pecuniary interests that

could bias their clinical decision making, such as commercial interests in pathology companies and their own clinical dispensaries.

COMPLEMENTARY MEDICINE PRODUCTS

Several thousand complementary medicine products are now available on the market, the vast majority of which are available without prescription. Choosing the best product, correct dose and time frame for use, and having realistic expectations of the treatment are just some of the factors that healthcare practitioners must consider before recommending a specific product (Table 6.1). These factors, which are addressed in further detail in the monographs and chapters of this book, must be considered in the light of each individual patient's circumstances, including their condition and co-morbidities, renal and hepatic function, personal preferences, financial resources and their ability to self-monitor their condition.

Complementary medicines in Australia are regulated in the same way as pharmaceutical medicines and are evaluated for quality and safety; however, seemingly similar products will vary with respect to their efficacy and supporting scientific evidence. Most complementary medicines are available over the counter (OTC) through pharmacies, health food stores and supermarkets; however, there are also certain complementary medicines that are available as practitioner-only products. These are prescribed and dispensed only by a CAM practitioner; they can have different potencies and formulations from those available OTC and include extemporaneously compounded herbs that require time, specific knowledge and expertise to dispense. Clearly, making product choices can be confusing, and clinicians should be encouraged to become familiar with

TABLE 6.1 Factors to Consider When Recommending a Complementary Medicine

Product factors	Comments
Mechanism/s of action	How well established are these? Do they seem plausible?
Evidence and expectations	Is it likely to achieve treatment goals? In what time frame? Do not rely on label claims alone. Consider the type of evidence available for this particular indication. For herbs also consider: extract and plant part/s tested. For nutrients: consider chemical form and bioavailability.
Dose and administration route	Ensure these are correct for the specific indication.
Frequency, timing and ease of use	Reduced frequency improves compliance. Consider timing, such as before, during or after meals.
Quality control standards	Not all countries impose high quality control standards on the manufacture of complementary medicines; e.g. the USA. In Australia, only use products with AUST L or AUST R numbers on the label.
Combination products or single entities	For combination products, consider dosage and potential synergy of individual ingredients.
Potential to induce adverse reactions	Consider potential likelihood of adverse reaction and consequence (see Chapter 7 for more information).
Potential to induce interactions	Are harmful, beneficial or neutral interactions possible? Should the product be avoided, used only under professional supervision, or actively prescribed? (Use METOPIA algorithm in Chapter 8.)
Contraindications	Take special care with high risk groups (see Chapters 7 and 10 for more information).
Storage	Consider sensitivity to light and heat, need for refrigeration, and shelf life.
Cost	Compare cost with that of other treatments — medicinal and non-medicinal.
Availability	Is it available OTC or only from a practitioner?

the products available and eventually identify a group of favoured products they feel confident in prescribing.

There are many good reasons for including complementary medicines into routine practice (Table 6.2). Medicines that are supported by good evidence of efficacy and safety, or which offer advantages over conventional medicines in terms of cost-effectiveness, should be considered an essential part of routine clinical practice. Indeed, there could be seen to be an ethical imperative for considering the use of such complementary medicines, as not to do so would deprive patients of potentially safe and effective treatments (see Table 6.3 and specific monographs for further details).

THE ROLE OF CAM IN THE NHS

In October of 2005, a report entitled *The role of CAM in the NHS* was published. This report examined whether other treatment approaches that are not funded by the National Health Service (UK) can provide some financial relief, while retaining good quality patient care (Smallwood 2005). The report was commissioned by HRH Prince Charles, who engaged a leading economist to investigate the potential contribution of mainstream complementary therapies to healthcare in the United Kingdom. The enquiry took more than 9 months and involved an assessment of the scientific evidence, interviews with experts, such as researchers, policy makers and healthcare professionals, and case studies to draw together published and experiential information, financial data and economic forecasting.

One area that was evaluated was acupuncture, as it is widely available through private and NHS-funded clinics. The studies examined by the enquiry suggest that acupuncture may have advantages in terms of costs and benefits in general practice for musculoskeletal conditions

TABLE 6.2 Reasons for Using Complementary Medicines

Efficacy — will alleviate symptoms of disease, reduce exacerbation or present a cure.

Safety — present a safer treatment option than other therapies.

Cost — when they provide lower cost treatment options.

Adjunct — if the efficacy and/or safety of other interventions can be improved with adjunctive use.

Prevention — when they provide safe prevention strategies in at-risk populations.

Enhance health — increase sense of wellbeing and quality of life.

Enlists patients' involvement in their own healthcare.

TABLE 6.3 Examples of Herbs and Natural Supplements with Proven Efficacy

Herb/natural supplement	Proven efficacy
Chaste tree	Premenstrual syndrome
Cranberry	Urinary tract infection prophylaxis
Fish oils	Cardiovascular disease prevention; lipid-lowering
St John's wort	Depression
Ginkgo biloba	Dementia
Glucosamine sulphate	Osteoarthritis: symptoms and disease progression
Hawthorn	Chronic heart failure (New York Heart Association classes I–II)
Honey	Infection control/wound healing
Horse chestnut	Chronic venous insufficiency
Kava kava	Anxiety
Peppermint	Irritable bowel syndrome
Probiotics	Preventing antibiotic-induced diarrhoea
Pygeum	Benign prostatic hypertrophy (BPH)
Saw palmetto	BPH
Tea tree oil	Topical infections

and when used as an adjunct to conventional treatment for lower back pain, migraine and stroke rehabilitation. With regard to herbal medicine, the enquiry identified several OTC herbal medicines that provide potential cost savings to the government, while offering similar or greater benefits than pharmaceutical treatments. Although many herbal medicines were not evaluated because of insufficient time, those named in the report are St John's wort, phytodolor, *Echinacea*, *Ginkgo biloba*, devil's claw, hawthorn, horse chestnut and saw palmetto.

DISPENSING PRODUCTS

The choice whether or not to stock and dispense products is a complex one, with ethical, commercial and practical issues to be considered. Many medical practitioners may feel it is unethical to profit from the sale of products they prescribe (Cohen et al 2005), but the direct dispensing and selling of complementary medicines by doctors is in line with the sale of products by other registered healthcare professionals such as veterinary surgeons, pharmacists, podiatrists, physiotherapists and optometrists. These healthcare professionals dispense advice and sell products in the same consultation, as do CAM practitioners such as naturopaths, herbalists and traditional Chinese medicine (TCM) practitioners.

The direct dispensing of products provides practitioners with some assurance of patient compliance and promotes the use of correct dosage, administration forms and extracts. This may be particularly important for herbal products. Direct dispensing is convenient for patients and gives them the confidence that a practitioner who is aware of their history and current needs has directed them to the best treatment. If a decision to dispense products is made, this should obviously be done in an ethical manner, and treatment plans must always be dictated by what is in the best interests of the patient.

Ethical conduct

The issues of ethical practitioner conduct have their basis in the Hippocratic oath, which acknowledges the inherent inequality of the practitioner–patient relationship and the responsibility of the doctor to use this to improve the health of their patients who may be vulnerable and who entrust themselves to medical care.

The ethical conduct of doctors has since been explored by various professional associations and colleges such as the Australian Medical Association and Royal Australian College of General Practitioners. The standards of ethical conduct (AMA 2004) include:

- always acting in the best interests of patients
- not exploiting patients for any reason
- respecting patients' right to make their own decisions and to accept or reject advice about treatment or procedures
- ensuring patients are aware of fees, and that healthcare costs are openly discussed and direct financial interests disclosed.

These standards also apply to IM, and the sale of complementary medicines must conform with these principles, insofar as the interests of the patient are the foremost consideration and patients are fully informed about the nature, benefits, risks and costs of any proposed treatment, as well as any financial interests of the practitioner. Patients also need to be aware that they have the right to accept or reject any advice (AMA 2004).

INFORMED CONSENT

The ethical precepts of informed consent and the respect for patient autonomy compel healthcare practitioners to inform their patients about the range of appropriate treatments available, their associated costs and risks, and to respect the right of patients to make their own decisions. In practice, this can be problematic, as it remains unclear how much information practitioners are expected to know themselves and how much patients require.

This issue has been addressed recently by the joint position statement on complementary medicine put out by the Royal Australian College of General Practitioners (RACGP) and the Australasian Integrative Medicine Association (AIMA):

> General practitioners require a basic understanding of natural and complementary medicine and should receive sufficient training in their undergraduate, vocational and further education to enable them to include natural/complementary medicines with proven safety and efficacy in their practice, and to discuss issues with their patients on an informed basis.
>
> The key principle of evidence based medicine should be the basis of evaluating natural and complementary medicines and their use by the medical profession. It should also be the basis of any collaborative relationships between general practitioners and complementary therapists.
>
> *RACGP/AIMA 2004*

Based on this statement it would seem reasonable that all general practitioners need to know enough about reasonably available complementary therapies to use safe and effective, evidence-based therapies where appropriate and to avoid predictable adverse events and interactions induced by commonly used complementary therapies. It has further been argued that doctors have an ethical and even a legal obligation to become familiar with this area and open a dialogue with their patients about complementary treatments to provide quality care and address safety concerns (Brophy 2003).

Unfortunately this is a difficult task, as most medical schools give little or no time to teaching about evidence-based complementary therapies, and the opportunities for vocational and postgraduate medical education about CAM remain limited. As a result, having ready access to quality, evidence-based, independent information sources is essential to guide clinicians when making healthcare decisions or faced with patient enquiries about CAM.

EVIDENCE-BASED MEDICINE

The idea that practitioners need to refer to evidence is the basis of evidence-based medicine (EBM), which has been described by Sackett et al (1996) as: 'the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients'. These authors go on to state:

> The practice of evidence-based medicine means integrating individual clinical expertise with the best available external clinical evidence from systematic research. By individual clinical expertise we mean the proficiency and judgment that individual clinicians acquire through clinical experience and clinical practice. Increased expertise is reflected in many ways, but especially in more effective and efficient diagnosis and in the more thoughtful identification and compassionate use of individual patients' predicaments, rights, and preferences in making clinical decisions about their care.

This statement acknowledges that, in practice, for most treatment decisions the conclusive evidence simply does not yet exist, and the best available evidence may simply be clinical experience or anecdotal reports. It is also clear that each practitioner and patient must seek out the necessary information they require and interpret this evidence in the light of each individual situation.

EVIDENCE IN PRACTICE

EBM adds another dimension to the art of medicine and requires clinicians to review the evidence of safety and efficacy for the therapy under consideration, as well as to understand the inherent limitations of the available evidence and its relevance to a specific situation. It also involves weighing up the evidence for a number of different therapies, which includes an assessment of their costs and risks versus their potential benefits (see PEACE mnemonic in Chapter 1).

In the specific case of CAM, a growing number of treatments have been subject to scientific investigation, with over 6000 RCTs identified and made available through the central Cochrane Library. Although this is encouraging, many therapies do not yet have established evidence and some remain difficult to assess under controlled conditions (e.g. massage). In practice this should not preclude them from being viable treatment options, but can place some limitations on use. Ultimately, clinical decision making should be guided by the evidence available (Fig. 6.1).

- When there is evidence of efficacy and safety for CAM, it should be recommended to patients where appropriate and included as part of standard care.
- When the efficacy of a treatment is unknown, due to insufficient investigation or inconclusive results, and there are no apparent safety concerns, patients deciding to use these therapies should be supported and supervised. It is prudent to set specific therapeutic objectives and time frames, and to monitor for potential adverse outcomes.

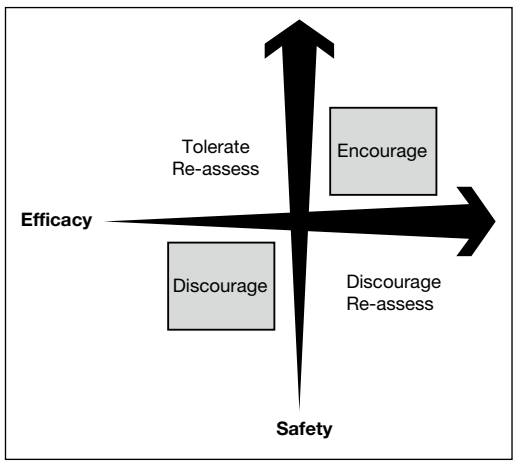

FIGURE 6.1 Paradigm of clinical decision making (Based on Renella & Fanconi 2006, adapted from Cohen & Eisenberg 2002)

- When there is evidence for a lack of effect, use should be discouraged, especially if there is the potential to induce adverse effects.

This approach is summarised by the four Ps: **P**rotect, **P**ermit, **P**romote and **P**artner (Jonas et al 1999). Thus practitioners need to protect their patients by ensuring the safety and cost effectiveness of treatments, permit therapies that are safe and inexpensive, even if their efficacy has not been conclusively proven, promote proven practices and partner with patients and other complementary therapists (Jonas 2001) (Table 6.4).

Complementary therapies with rigorous evidence for efficacy and safety that do not require specialised skills or expertise to implement should be considered part of mainstream practice and used by all healthcare practitioners, whereas other therapies/medicines with less rigorous evidence or requiring specific expertise may be more appropriately used by those with a special interest and/or appropriate training. Therapies that have evidence for a lack of efficacy and safety should be abandoned to the long list of therapies that have been discontinued throughout medical history.

A MULTIDISCIPLINARY, COLLABORATIVE APPROACH

While it remains unclear which therapies should be considered within the domain of every doctor and which should be considered areas of special interest or the exclusive domain of CAM practitioners, it is clear that the practice of IM requires a multidisciplinary approach with collaboration and communication between the different practitioners with declared interests and expertise who are aware of their own limitations. It is also clear that whether or not doctors are prepared to personally use CAM, all doctors need to be prepared to discuss their use and inform patients of viable evidence-based options, as well as assess the likelihood of safety issues or interactions.

OPEN COMMUNICATION

Effective communication and teamwork is essential for the delivery of high-quality, safe patient care: communication failure is an extremely common cause of inadvertent patient harm.

Numerous surveys have shown that patients commonly combine CAM with conventional medical treatments, outside the knowledge of their various healthcare providers. This may be particularly true in hospitals, where it has been found that while almost 50% of surgical patients take complementary medicines in the peri-operative period, 80% are not asked about this use (Braun et al 2006). It is also estimated that more than 50% of users of CAM do not disclose this use to either their hospital doctors (Braun et al 2006) or their GPs (MacLennan et al 2002). In addition, many treatments are patient-initiated without professional advice.

According to a review of 12 studies, patients do not disclose use of CAM to their medical practitioner for reasons that can be grouped

TABLE 6.4 Principles for Advising the use of Complementary Therapies

Status of evidence	Special skill/training required	Special skill/training not required
Strong evidence for quality, safety and cost-effectiveness	*Promote & partner with therapist* Encourage/recommend/implement therapy. *OR* Refer to appropriate practitioner and/or consider obtaining required skills (e.g. acupuncture).	*Promote & partner with patient* Encourage/recommend/implement therapy. Consider as part of standard practice (e.g. dietary modification).
Insufficient or inconclusive evidence for quality, safety and cost-effectiveness	*Permit & partner with therapist* Continue therapy with caution and monitor patient in collaboration with other practitioner if necessary. *OR* Consider more appropriate therapies.	*Permit and partner with patient* Continue therapy with caution and monitor patient. *OR* Consider more appropriate therapies.
Strong evidence against quality, safety and cost-effectiveness	*Protect & partner with patient* Discourage use. Discuss reasons and desired outcomes and consider more appropriate therapies.	

into three main themes (Robinson & McGrail 2004).

1. Concerns about eliciting a negative response, disapproval and rejection. Patients fear they will be persuaded to cease use and the practitioner will not continue to provide patient care.
2. Patients believed that the practitioner does not need to know about CAM use because it was irrelevant to the biomedical model of treatment; their practitioner was ignorant about CAM and would not be able to understand why it was being used or be able to contribute useful information about it.
3. Not being asked about CAM use or perceiving practitioner disinterest in the topic. (This has proved to be more significant in preventing discussion than previously thought [Braun et al 2006].)

It is therefore not unusual for there to be little coordination between patient-initiated and clinician-initiated treatments, which can result in suboptimal 'integrative care' and potentially unsafe outcomes.

As the popularity of CAM continues, medical practitioners in the community and hospital settings will continue to come into contact with patients who are using, or considering using, these treatments, making the issue of communication and competence in dealing with CAM-related issues more urgent. Asking patients about possible use of complementary medicines may seem daunting; however, it is a necessary measure to promote patient safety. It also provides an opportunity to gain insight into patients' beliefs and attitudes, as well as their willingness to be involved in their own healthcare.

Although discussions about complementary therapies may enhance the therapeutic relationship, non-disclosure can indicate a serious deficiency in this relationship, for if patients are unwilling to discuss their use, it is also possible that they will not discuss other personal information that may have an impact on their health and medical treatment. Non-disclosure also refers to a lack of interdisciplinary communication. Although many patients would like to benefit from treatment and advice from both doctors and natural therapists, effective collaboration between these groups appears to be limited and it has been estimated that of the 44% of Australians who visit natural therapists, only 13% do so on the advice of their doctors.

INTERDISCIPLINARY COLLABORATION

True collaboration can occur only in an environment of shared respect and trust, and knowledge of what can be offered. In reality, both medical and CAM practitioners have several concerns about each other's practice, which must be addressed in order to achieve a good working partnership.

For medical doctors, there are concerns that CAM practitioners may put patients at risk of delayed or missed diagnosis and/or delay the use of more effective therapies (Cohen et al 2005). There is also concern that CAM practitioners might encourage patients to refuse use of 'proven' treatments in preference for 'unproven' ones, particularly in serious diseases such as cancer or HIV-AIDS. The promotion of implausible or untrue claims or unsafe complementary therapies that waste patients' time and money, or induce adverse events, is another source of apprehension.

Complementary therapists on the other hand may be concerned that medical doctors too readily prescribe symptom-suppressing drugs, yet do little to address underlying causes and support natural homeostasis through diet, lifestyle and preventive approaches. There is concern that patients may waste their time and money on treatments that exert significant side effects while providing limited benefits, and that medical practitioners may advise against the use of natural therapies because of fear, ignorance or arrogance. Furthermore, natural therapists may be concerned that their positions are being usurped by doctors who take on the use of natural and complementary therapies with little specific training and little consideration for their underlying philosophies and holistic considerations (Cohen 2001).

Many of these concerns are based on ignorance and misunderstanding between the practitioner groups and can be addressed through open and honest communication and formalised communication strategies, one of the most important of which is through the provision of formal correspondence in referral letters.

Referral letters

Referral letters are a standardised method of professional communication between practitioners. They can be outgoing to another practitioner or incoming from another practitioner; they set out what has been done to date and any specific requests. Referral letters may request a second opinion, ask for help in patient management through a collaborative approach or transfer patient care (Table 6.5). Upon

receiving a referral letter, a practitioner is expected to send return correspondence, thanking the referring practitioner for the referral and stating the details of any procedures undertaken, new findings, clinical impressions or recommendations, as well as their rationale, and arrangements for follow-up. Such correspondence forms an essential part of professional collaboration and may also have legal status as part of the medical record and/or eligibility for funding or patient reimbursement. It also ensures that practitioners understand each other's expectations and goes far towards fostering goodwill and mutual respect.

Although effective communication is vital, there are still many issues that need to be resolved before interdisciplinary collaboration between complementary and conventional practitioners becomes the norm. These include the credentialling and regulation of CAM practitioners, differences in nomenclature between disciplines, equity of access in different healthcare settings, the requirements for evidence-based practice, appropriate funding models and medico-legal issues including referrals and vicarious liability (Cohen 2004). Despite these obstacles the fruits of interdisciplinary collaboration are becoming evident with the emergence of clinics in which doctors and natural therapists share premises and work together for the benefit of their patients. Currently this collaboration and drive towards IM seems to be in response to patient demand rather than driven by professional associations, government policy or the accumulation of supportive scientific evidence.

Patients' responsibility

Patients now have unprecedented access to healthcare information, as well as unprecedented power to choose the type of services they receive. This power is further supported by the ethical principle of informed consent and respect for patient autonomy. With power, however, comes responsibility. Patients must therefore begin to accept the responsibility to become more informed and to be active participants in the decision making process and the implementation of their healthcare. This responsibility also extends to implementing lifestyle interventions as summarised by the SENSE approach (see Chapter 1). Thus in every encounter, whether patients are currently well, at risk of disease or have an established disease, practitioners should take the opportunity to enlist patients' cooperation in implementing their own healthcare and discussing interventions that can be used to enhance health, prevent disease and complement the use of any disease-specific interventions.

PERSONAL AND PROFESSIONAL SATISFACTION

The role of the IM practitioner is particularly challenging and rewarding. It compels practitioners to develop multiple skills, be informed

TABLE 6.5 Elements of a Referral Letter

Element	Details
Professional letterhead	Referring practitioner's name Qualifications Practice address Phone number/fax/email Provider number if appropriate Date of referral
Practitioner and patient identification	Details of practitioner to whom referral is being made Patient identifying details: full name, date of birth, address, hospital UR (patient) number etc
Patient's history	Brief patient history including background, any special considerations, past history and present complaints Investigations, treatment to date, including current and/or proposed treatments pharmaceutical or complementary, rationale and expected outcomes including involvement of other practitioners Any psychosocial concerns
Reasons for referral	Detailed reasons for referral, including expected actions of other practitioner (e.g. second opinion, further investigation, specific intervention, help in case management, transfer of care etc)
Conclusion	Arrangements for follow up Referring practitioner's signature

about many therapies, navigate between different information sources and practitioners, and keep an open mind. It also broadens the capacity of practitioners to deal with a great variety of patient issues from a number of perspectives, thus providing continuous intellectual stimulation and both professional and personal satisfaction. To have people's confidence as a practitioner and to participate in their most emotionally charged moments, which may include both the beginning and the end of their life, is a great privilege. Sharing the triumphs and tragedies of individuals from different walks of life is a great reward and practitioners' personal lives are undoubtedly enriched.

Our knowledge of health and disease is far from complete, and healthcare practitioners regularly deal with uncertainty. The implementation of IM, however, recognises that compassion is always helpful and healing is always possible, even when curing is not (Rakel & Weil 2003); it also recognises that practitioners endeavour always to do their best with what they have from their perspective and to be comfortable in the knowledge that their best will continually get better.

SUMMARY POINTS

- Taking time to develop a good therapeutic relationship may be therapeutic in itself and provides the best foundation for any other therapy.
- The integrative approach compels practitioners to develop an intimate understanding of their patients' lives, and to provide social support, understanding and compassion.
- The widespread use of complementary therapies compels doctors to discuss their use with patients and to do so on an informed basis and in a non-judgmental manner.
- All healthcare practitioners should have access to appropriate and independent information, so that they can provide sound advice and detect predictable interactions and safety issues.
- Healthcare practitioners need to be aware of their particular biases, limitations and financial interests, and to clearly state these to patients when patient care may be affected.
- Healthcare practitioners should attempt to make patients active participants in the decision-making process and the implementation of their own healthcare.
- Healthcare practitioners need to liaise with different practitioners in order to advise on and implement the most appropriate interventions.
- Complementary therapies/medicines with rigorous evidence for efficacy and safety that do not require specialised skill or expertise to implement should be considered as part of mainstream practice.
- When efficacy of treatment is unknown and there are no apparent safety concerns, patients deciding to use these therapies should be supported and supervised.
- Therapies/medicines with less rigorous evidence or requiring specific expertise may be more appropriately used by healthcare practitioners with a special interest and/or appropriate training.
- When there are differences in the supporting evidence and quality of different herbal extracts and other CAM, the recommendation of specific brands of CAM products may be appropriate.
- Compassion is always helpful and healing is always possible, even when curing is not.

> By fostering interaction, cross-disciplinary research, and collaborative care, redefined standards of care will emerge that are scientifically based and interdisciplinary in nature. The outgrowth of such a paradigm shift will change the legal and practice environment from one of fear to freedom.
>
> *Engler et al 2009*

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CHAPTER 7
SAFETY OF COMPLEMENTARY MEDICINES

Complementary medicines (CMs) are widely used by the public, who assume they are a safe, non-pharmaceutical option that can be used to prevent, treat and manage disease (MacLennan et al 2002). The perception that CMs are safe is largely based on the assumption that if something is 'natural' it is inherently safe, a view encouraged by many in the health food industry. Unfortunately the 'natural' argument is simplistic and not well thought out, because nature provides many examples of unsafe substances, such as the naturally occurring poisons hemlock, jimsonweed and oleander. There is also an assumption that possible side effects and toxicities will be listed on product labels and therefore, if the information is absent, the product must be well tolerated. In Australia, some warnings are required on labels; however, CMs are not accompanied by comprehensive consumer product information (CPI) in the same way as many pharmaceutical medicines; many CMs are self-selected without professional advice, which means that much-needed information is not delivered with the product (Jamison 2003, MacLennan et al 2002).

Importantly, people who use CMs tend to have poorer health than the general community (MacLennan et al 2006) and are not necessarily dissatisfied with their conventional care (Astin 1998), which raises the possibility of dual care by complementary and conventional medical practitioners. This situation is not necessarily dangerous and can produce significant benefits when well coordinated; however, if communication is poor, and complementary and conventional practitioners remain unaware of what the other has recommended, a potentially unsafe situation can arise. The prospect of interactions or adverse drug reactions leading to misdiagnosis, induction of withdrawal effects and misleading pathology test results are examples of unwanted outcomes when combined care is not coordinated.

In the real world, people are exposed to risk whenever they actively choose to undertake a treatment or choose to do without. Some risks are identifiable, while others are unknown. In practice, in order for patients to make an informed decision, these risks must be classified into those that are acceptable and those that are unacceptable, and then considered against the potential benefit, Over-the-counter (OTC) CMs offer a lower-risk and potentially more cost-effective option than other treatments for some indications and are generally considered safe when used appropriately under 'normal' circumstances; however, they are not entirely devoid of risk.

A BRIEF HISTORY OF MEDICATION SAFETY

The potential for medical care to cause harm has been appreciated throughout history. In ancient times, knowledge of medicine, pharmacology and the healing arts developed through trial and error, with many adverse outcomes and deaths along the way. Although both practitioners and patients were aware that health could be compromised by the 'cures' used to alleviate disease, it was in ancient Greece that patient safety was formally acknowledged as the highest priority. The maxim *primum non nocere* (First, do no harm) is attributed by some historians to Galen (AD 131–201) and is still a basic tenet of modern medical practice (Ilan & Fowler 2005).

As societies developed over the centuries, so too did their systems of medicine and healing — particularly the Vedic system of medicine, which originated more than 3000 years ago in India, and Chinese medicine, which has an appreciation of the importance of dosage. Persian medicine had a major influence on the development of medicine in the Middle East and Europe, most notably with *The canon of medicine* written by the Persian scientist Avicenna (AD 980–1037) in the 11th century. This major work documented 760 medicines, made comments about their use and effectiveness, and remained a standard medical text in western Europe for seven centuries. Avicenna recommended the testing of new medicines on animals and humans before general use, no doubt in recognition of their potential to have both beneficial and harmful effects.

In medieval Europe, there was a mixture of scientific and spiritual influences on the practice of medicine, so factors such as destiny, sin and astrology played a role in perceptions of health and disease. Two major trends appeared during this period, as the practice of medicine developed among both physicians of the upper classes and folk healers who lived in the villages. From the 14th to the 17th centuries, monasteries played a major role in the provision of medicine and developed great expertise in pharmacognosy. At the same time, the Christian church was instrumental in eliminating much of the practice of folk medicine through its witch-hunts, which many believe retarded the development of medicine.

In the 16th century, Paracelsus (1493–1541) was one of the first physicians to believe that chemicals could cure and cause certain illnesses. He determined that specific chemicals were responsible for the toxicity of a plant or animal poison, and documented the body's responses to those chemicals. Paracelsus then concluded that the body's response was influenced by the dose received. He further discovered that a small dose of a substance may be harmless, or even beneficial, whereas a larger dose can be toxic. In essence, he started expounding the concept of a dose–response relationship. Paracelsus made an enormous contribution to medicine when he stated plainly, 'What is there that is not poison? All things are poison and nothing (is) without poison. Solely the dose determines that a thing is not a poison' (Watson 2005). As a result, he is sometimes referred to as the 'Father of Toxicology'.

In practice, this refers to the biological effect of chemicals that can be either beneficial or deleterious. Which of these effects occurs depends on the amount of active material present at the site of action (internal dose), and the concentration of the amount present relates to the amount of substance administered (external dose).

During the 18th and 19th centuries deliberate clinical testing of medicines began, and the study of dose–response relationships led to the safer use of medicines. From the 19th century onwards, developments in pharmacology, physiology and chemistry meant that drugs could be artificially synthesised and be produced by large-scale manufacturing. During this time, animal- and plant-based medicines began to be replaced in clinical use by mass-produced pharmaceutical medicines that were being newly created in laboratories or synthesised from traditional medicines (e.g. morphine from *Papaver somniferum*).

Up to this point, Western herbalism had been intrinsically linked to the practice of medicine, and herbal products were an important source of treatment. Empirical knowledge accumulated and formed a body of evidence now referred to as 'traditional evidence', a knowledge base built on the basic tenets of good clinical practice (i.e. careful observation of the patient, the environment and the diseases). This huge and diverse store of learning includes not only prescriptions for health, but also safety information. The traditional evidence base is still expanding and becoming more accessible as researchers investigate and document various healing practices worldwide. Although traditional evidence provides a valuable starting point, it has many limitations, especially with regard to issues of safety. Careful patient observation is likely to detect immediate or serious adverse effects, but is less likely to identify slow-onset responses or mild to moderate side effects that could be considered symptoms of a new disease. Additionally, many medicinal preparations contained multiple ingredients, making it difficult to identify which one might be responsible for inducing an adverse reaction.

More recently, the traditional evidence base has been joined by a scientific evidence base, which provides additional information about pharmacological actions, clinical effects and safety; however, much still remains unknown.

Clinical note — History of poisons

The history of poisons dates back to the earliest times, when humans observed toxic effects in nature, most likely by chance. By 1500 BC, written records indicate that the poisons hemlock, opium and certain metals were used in warfare and in facilitating executions. Over time, poisons were used with greater sophistication; notable poisoning victims include Socrates, Cleopatra and Claudius. Today, the 'science of poisons' is known as toxicology. This field of learning investigates the chemical and physical properties of poisons and their physiological or behavioural effects on living organisms, and uses qualitative and quantitative methods for analysis and for the development of procedures to treat poisoning (Langman & Kapur 2006). The 20th century was marked by an advanced understanding of toxicology; DNA and various biochemicals that maintain cellular functions were discovered, so that today we are discovering the toxic effects on organs and cells at the molecular level.

This is particularly true regarding the safety of CMs in children and in women who are pregnant or lactating, and concerning drug interactions, which is a relatively new phenomenon. Just as Galen pronounced hundreds of years ago, 'First, do no harm' should remain the practitioner's guide.

WHAT IS SAFETY?

Safety is a complex issue that is determined by considering the interaction between 'likelihood' and 'consequence'. These two variables will differ for each medicine and individual. The likelihood can be graded from 'near impossible' to 'certainly likely', and the severity of consequence can be graded from 'negligible' to 'serious and life-threatening', with many outcomes lying somewhere between these extremes (Fig 7.1).

With regard to medication safety, avoidance of an adverse drug reaction (ADR) is paramount. Several factors are associated with an increased likelihood of developing an ADR, such as advanced age and polypharmacy, but most ADRs occur in people who are prescribed treatment within the limits of accepted clinical practice (Burgess et al 2005).

BENEFITS, RISK AND HARM

Many different sources of risk are associated with therapeutic products:

- **The product itself** — side effects and toxicity of ingredients, administration form, potential harm through excessive dosage and length of time used.
- **Manufacturing factors** — poor manufacturing process, which introduces contaminants, uses unsafe excipients or incorrect ingredients etc.
- **Prescribing faults** — incorrect product prescribed, based on insufficient information about it, the patient or the disease, or simply negligence.

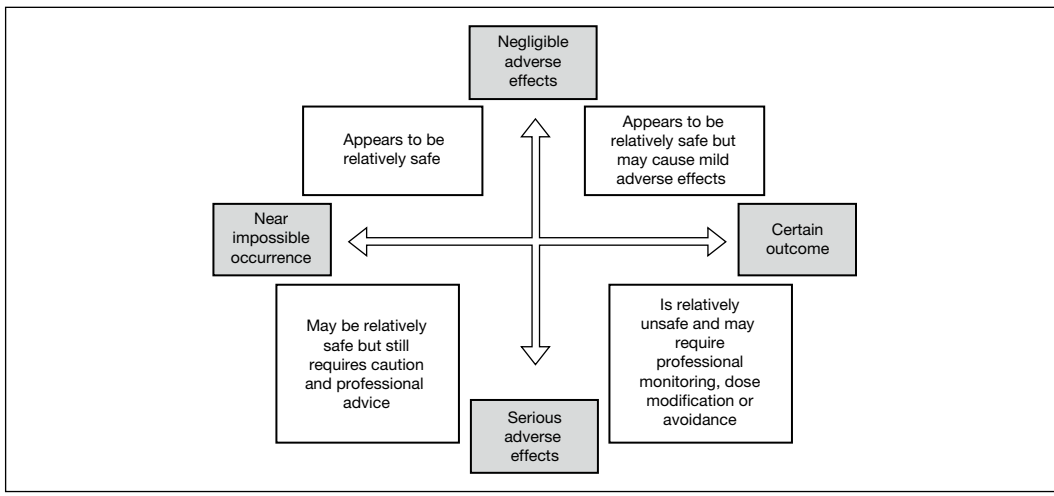

FIGURE 7.1 Interaction between the two variables of 'likelihood' and 'severity of consequence' with regard to medication safety

- **Patient factors** — incorrect use of a product when information for appropriate use is poorly understood, or insufficient or inappropriate self-diagnosis and treatment.

Whenever a treatment is chosen, it is done so in the belief that its potential benefit will outweigh its potential to cause harm. Practice guidelines and traditions provide guidance when making risk–benefit evaluations and are based on common treatment decisions made many times before by many clinicians, together with the available evidence. The safety information tends to come from a variety of sources, such as post-marketing surveillance and spontaneous reporting schemes, laboratory and animal studies, anecdotal reports, theoretical reasoning and, increasingly, formal studies.

The amount of safety literature published on pharmaceutical medicines is overwhelming. It has been estimated that 30% of the primary published literature about ADR appears in anecdotal reports and 35% as formal studies or randomised controlled trials (Aronson et al 2002). As regards the safety of complementary medicines, traditional evidence and theoretical reasoning are heavily relied upon to provide guidance because relatively little reliable information has been published in the peer-reviewed literature. This poses a challenge for practitioners when making a rational decision about the relative risks of treatment and is one of the great difficulties of CAM practice. For the public who are interested in using OTC products, it is just as difficult to find reliable and understandable information about their safety and efficacy.

ADVERSE DRUG REACTIONS (ADRs)

The World Health Organization defines an ADR as a 'response to a medicine which is noxious and unintended that occurs at doses normally used in humans'. When two medicines interact in a way that produces an unwanted effect, this is also referred to as an ADR. Adverse reactions have been classified into different types depending on severity and likelihood or onset of reaction, and do not always result in serious outcomes; however, an ADR is considered serious when it is suspected of causing death, danger to life, admission to hospital, prolongation of hospital stay, absence from productive activity, increased investigational or treatment costs, or birth defects.

Adverse reactions can arise from either an intrinsic or an extrinsic effect. An intrinsic effect refers to the active ingredient itself, such as the herbal medicine present within a product, whereas an extrinsic effect relates to product characteristics resulting from poor manufacturing processes or quality control, such as contamination and adulteration. Intrinsic adverse effects can be categorised in a similar way to pharmaceutical medicines and are mainly type A or type B reactions.

Type A reactions

Type A reactions are the most common form and are typically dose-related, predictable from the known pharmacology of the medicine, associated with high morbidity but low mortality, and potentially avoidable (Routledge et al 2004). People most at risk of a type

TABLE 7.1 Potential Risks Associated With the Use of Complementary Medicines

Type of harm	Circumstances
Delay in diagnosis	When a patient has avoided or delayed seeking medical advice because they are self-treating with CMs. When a complementary medicine practitioner has not referred a patient to a medical practitioner for early diagnosis.
Adverse effects	Increased risk of adverse reactions with inappropriate use of CM products or when patients self-select CM products without professional advice. Increased risk if products used are not manufactured to pharmaceutical grade quality.
Drug interactions	Increased risk of drug interactions when patients: (a) self-select CM products without professional advice; (b) do not disclose use of CM products to their pharmacist or medical physician; (c) do not disclose use of pharmaceutical drugs to their CM practitioner.
Financial cost	If an expensive medicine or therapy is not providing benefits and a patient continues to use it, this presents an unnecessary financial burden.
Lost opportunity to treat	Failure to undertake a different treatment with proven benefits, when the current treatment is ineffective but is being used to the exclusion of others.
False hope of a cure	When cure is unlikely, the use of any medicine or therapy that is associated with false hope may delay important considerations, such as attending to 'unfinished business'.

A reaction are frail, older patients who are also likely to be receiving a combination of medicines and those with altered hepatic or renal function. There is now mounting evidence to indicate that some type A adverse reactions are due to genetic polymorphisms, which affect an individual's drug clearance rate and therefore toxicological response. This may explain why certain individuals taking medicines in the recommended doses experience adverse reactions, whereas the majority of the population does not. Examples related to pharmaceutical medicine are bleeding with anticoagulants and hypoglycaemia with the use of insulin. An example for herbal medicine is licorice-associated hypertension, which is thought to be caused by increased renal sodium retention. The glycyrrhetinic acid in licorice inhibits renal 11-beta-hydroxysteroid dehydrogenase type 2 and, by that mechanism, increases the access of cortisol to the mineralocorticoid receptor that causes renal sodium retention and potassium loss. If continued for sufficient time, clinically significant changes in blood pressure and potassium status develop, which can be avoided by recommending that high-dose licorice herbal products not be used for longer than 2 weeks (Heilmann et al 1999). In recognition of this adverse effect, some manufacturers produce licorice products that do not contain glycyrrhetinic acid, so that they can be used more safely in the long term.

Table 7.2 gives some examples of known or suspected type A adverse reactions to herbs and natural supplements. For many herbal and natural medicines, there is insufficient reliable information about possible adverse reactions; where available, evidence from clinical trials, case reports and post-marketing surveillance systems are the main sources of information used in this book.

Type B reactions

Type B reactions are idiosyncratic and uncommon, difficult to predict and not dose related. They tend to have higher morbidity and mortality than type A reactions and are often immunologically mediated (Myers & Cheras 2004). Other factors contributing to type B reactions are receptor or drug metabolism abnormalities and the unmasking of a biological deficiency (e.g. glucose-6-phosphate dehydrogenase deficiency) (Bryant et al 2003). They do not appear to relate to genetic polymorphisms.

An example of a type B reaction to a pharmaceutical drug is interstitial nephritis with the use of NSAIDs. With regard to CMs, *Asteracaea* dermatitis provides a good example of a type B hypersensitivity reaction — specifically, an allergic contact dermatitis caused by exposure to allergens from the Asteraceae family or the daisy group of plants and plant extracts. Some examples of common plants that belong to this family are arnica (*Arnica montana*), chamomile (*Chamomilla recucita*), marigold (*Calendula officinalis*), echinacea (*Echinacea* spp), tansy (*Tanacetum vulgare*), feverfew (*Tanacetum parthenium*) and yarrow (*Achillea millefolium*). The most important allergens in the Asteraceae family are the sesquiterpene lactones, which are present in the oleoresin fraction of the leaves, stems, flowers and possibly pollen (Gordon 1999). The condition is most frequently seen

TABLE 7.2 Examples of Known or Suspected Type A Adverse Reactions to Herbs and Natural Supplements

Herb or natural supplement	Adverse effect/s
Andrographis paniculata	Vomiting, anorexia and gastrointestinal discomfort
Creatine	Nausea, vomiting, cramping, dehydration, fluid retention
Trigonella foenum (fenugreek)	Diarrhoea, flatulence
Fish oils	Gastrointestinal discomfort, diarrhoea
Allium sativum (garlic)	Breath and body odour, nausea, dyspepsia, flatulence, diarrhoea, increased bleeding
Zingiber officinale (ginger)	Gastric irritation, dyspepsia
Camellia sinensis (green or black tea)	CNS stimulation
Gymnema sylvestre	Hypoglycaemia
Paullinia cupana (guarana)	CNS stimulation
Selenium	Nausea, vomiting, irritability, fatigue, nail changes

TABLE 7.3 Examples of Known or Suspected Type B Adverse Reactions to Herbs and Natural Supplements

Herb or natural supplement	Adverse effect/s
Andrographis paniculata	Urticaria
Aloe vera	Hypersensitivity and contact dermatitis
Chamomilla recutita	Asteraceae dermatitis
Echinacea spp	Asteraceae dermatitis and anaphylaxis
Tanacetum parthenium (feverfew)	Asteraceae dermatitis — lip swelling, mouth ulceration and soreness when the leaves are chewed
Zingiber officinale (ginger)	Contact dermatitis with topical use
Thymus vulgaris (thyme)	Contact dermatitis with topical use of the oil

in middle-aged and elderly people; it typically starts in summer and disappears in the autumn or winter. The dermatitis manifests as eczema and can develop from exposure to airborne particles, direct topical application (such as cosmetics, perfumes, essential oils) or oral ingestion of allergenic components. The diagnosis of allergy can be difficult to establish, because there are few completely reliable laboratory tests and sometimes symptoms can mimic infectious disease symptoms. Table 7.3 gives examples of known or suspected type B adverse reactions.

Extrinsic factors

Extrinsic factors are also a consideration and of particular relevance when medicinal products are not manufactured according to the standards of good manufacturing practice, such as some produced in the USA and various Asian countries.

REGULATION AND PRODUCT INFORMATION

Numerous regulations are in place in Australia and New Zealand to protect people from potentially unsafe and dubious therapeutic products. Both countries have an international best-practice, risk-based regulatory system that encompasses both complementary and pharmaceutical medicines. Currently the Therapeutic Goods Administration (TGA) regulates the system in Australia, and aims to ensure the safety and quality of products and the truthful labelling of therapeutic goods. All products are entered onto the Australian Register of Therapeutic Goods (ARTG) and allocated an AUST L number if considered low risk (most CM products) or AUST R number if considered high risk, or low risk with a high-level claim (prescription drugs and many OTC pharmaceutical medicines). Products with either an Aust L or an Aust R number have been evaluated for safety and quality, whereas those with an AUST R number have also been evaluated for efficacy. Importantly, the TGA does not undertake the evaluation itself but relies on sponsors to provide the evidence.

The TGA also acts to ensure that all therapeutic products (complementary and pharmaceutical) are produced according to the code of Good Manufacturing Practice (GMP), and both licenses and audits manufacturers. Since the Pan Pharmaceuticals debacle in 2003, when more than 1000 CM products were recalled owing to quality control concerns, there have been calls for more frequent auditing of manufacturers in order to maintain closer control over product quality.

It appears that many people are unclear about the TGA's role in this regard and think it has a greater capacity to monitor product quality than actually occurs. According to a recent survey of more than 3000 people living in South Australia, approximately half assumed that CMs were independently tested by a government agency (MacLennan et al 2006).

It is important to note that the regulation of therapeutic goods varies greatly between countries and is influenced by ethnological, medical and historical factors. For instance, CM products are treated as foods by the Food and Drug Administration in the USA and not required to be manufactured to the same quality-control standards as pharmaceutical medicines (Brownie 2005).

RELIABLE INFORMATION SOURCES

When it comes to sources of information about herbal and natural medicines, a 1999 Australian consumer report found that 51% of people surveyed ask their friends or relatives for advice, with their mothers ranked as number one for healthcare advice (and it is open to debate as to where the mothers get their information from). In 2001, an Australian rural survey produced similar results, finding that

64.5% of people first ask family and friends for advice (Wilkinson & Simpson 2001). Interestingly, 78% of nursing, pharmacy or biomedical science students had used CAM in the previous 12 months, and 56% had visited a CAM practitioner. They, too, cited friends and family as their main sources of information (Wilkinson & Simpson 2001).

In recent years information technology has revolutionised the availability of health information for both practitioners and their patients. Besides relying on traditional sources of health information, such as healthcare providers, family and friends, people now have easy access to a variety of sources, particularly since the advent of the internet, email and text messaging.

Advertising plays a role in informing consumers about therapeutic products and is regulated by the government. Advertisements must comply with the Therapeutic Products Advertising Code and Therapeutic Product Act(s) and Rules, which state that advertising must be truthful, balanced and not misleading, and promote responsible use, and that the claims must be substantiated. The regulations relate to advertisements disseminated in all forms of media, including emails, websites and SMS messages. However, some information routes are exempt: bona fide news, editorial, public interest or entertainment programs are not restricted by the code, allowing for freedom of speech, but also allowing for sensationalism and inaccuracies.

In 2000, a study published in the *New England Journal of Medicine* found that media coverage of new drugs often exaggerates their benefits and downplays the associated risks (Moynihan et al 2000). The study analysed a sample of 207 stories released by 40 media outlets (36 newspapers, 4 television networks) that appeared between 1994 and 1998. Of the stories reviewed, 40% did not report benefits quantitatively and, of those that did, 83% used statistics to exaggerate the beneficial effect of the drug. Potential harm associated with use of the drug was not mentioned in 53% of stories, and 70% failed to mention costs. Based on the results of this study, it was concluded that news-media stories about medicines may be inadequate or incomplete regarding benefits, risks and costs, and may fail to disclose financial ties between researchers and pharmaceutical companies.

It is clear that a number of factors influence the way journalists report health issues in the news media. One important factor relates to the information provided (or not provided) to the journalist by a medical journal, researcher or company in a press release. The following case about the safety of *Echinacea* provides a local example. In 2002, an article entitled 'Adverse reactions associated with Echinacea — the Australian experience' was published in a scientific journal. It described in detail five allergic reactions to different *Echinacea* preparations, further stating that 51 adverse reaction reports involving *Echinacea* had been reported to the Adverse Drug Reactions Advisory Committee (ADRAC) (Mullins & Heddle 2002). This was then reported in the news media as alarming and drew much debate about the safety of herbal medicines in general. Inspection of the original article reveals that the reports were collected over a 21-year period, an important fact that failed to be included in the original press release (Flinders Medical Centre 2006).

A study published in the *Journal of the American Medical Association* suggests that incomplete or inaccurate press releases may be more common than once thought (Woloshin & Schwartz 2002). The study assessed the quality of press releases from seven high-profile journals, which were selected for their professional influence and because they are frequently cited by the news media. It was identified that for 544 articles published in the journals over the study period, 127 press releases were issued. Of these press releases, only 23% reported study limitations, 65% quantified study results and only 22% reported the source of funding.

Ideally, journalists, program researchers and writers involved in the media need to be able to assess the scientific information provided to them, and then present it accurately to consumers in a way that is easy to understand, unambiguous and not misleading, so that they can make better personal health decisions. Inaccurate, incomplete and inconsistent information not only confuses consumers, it also confuses healthcare providers and makes it difficult for them to determine which resource is useful and reliable.

A recent study by the National Prescribing Service in Australia found that both general practitioners (GPs) and pharmacists seek or need information regarding complementary medicines, and are particularly interested in information about drug interactions, adverse effects, contraindications and evidence of effectiveness. GPs tend to refer to trade journals, MIMS, the internet in general, and

peer-reviewed medical journals for information about CMs. Pharmacists' most common sources were the internet, MIMS and the Australian Pharmaceutical Products (APP) guide, colleagues and complementary medicine textbooks (Brown et al 2008). Interestingly, when asked which information sources were considered moderately or highly useful, CM textbooks came out on top for both groups of healthcare professionals. This implies that practitioners who only used standard drug information sources were not accessing the most useful resources available. Another consequence is the assumption by these practitioners that either little evidence exists (because little is available in standard pharmaceutical or medical texts or journals), or that there are no good resources.

Similarly, a study funded by the Department of Health and Ageing and the Pharmacy Guild that investigated the quality use of medicines in relation to complementary medicines found that pharmacists have trouble locating information they consider credible, and are keen for standardised information to be endorsed by a reputable organisation and made widely available.

MEDICAL DATABASES AND TEXTS: INCONSISTENCY

Unfortunately, some medical databases and textbooks that are widely used in the hospital system and universities are not always up to date; authors don't critically examine the evidence from primary sources and sometimes overstate the safety issues without considering the wider perspective. This makes it extremely difficult for a busy clinician to find accurate information in a timely manner.

An example presented here is the purported interaction between ginkgo biloba and warfarin. Ginkgolides found in ginkgo leaf inhibit platelet aggregation according to in vitro and ex vivo studies. As a result, it has been assumed that the effect is clinically relevant, and ginkgo has been implicated as the causative factor in case reports where haemorrhage has been described in association with ginkgo use (Koch 2005). It has also led many writers and clinicians to assume that a pharmacodynamic interaction exists between ginkgo and drugs affecting haemostasis at the platelet level (Bone 2008). Evidence from multiple controlled studies published over the last 5 years casts doubt on the clinical significance of this theoretical interaction, indicating it is unsubstantiated (see monograph on *Ginkgo biloba* for further details). Major databases and textbooks on complementary medicines provide quite different information to readers about this issue, adding to the confusion (Table 7.4, p 88).

ADR INCIDENCE

Alarmingly, the rates of ADR-related hospital admissions are rising and account for considerable morbidity, mortality and costs. One recent Australian study found that one in ten patients who visited a GP had experienced a significant ADR within the previous 6 months, and almost 50% of these were assessed as moderate to severe by the GP (Miller et al 2006). An ADR is more likely to be experienced with increasing age, peaking at 65 years and older, and by females rather than males. Children aged between 1 and 4 years are three times more likely to have an ADR than children in other age groups. At this rate, ADRs rank as one of the most important causes of morbidity. Anticoagulants, NSAIDs and cardiovascular medicines feature prominently as preventable, high-impact problems in Australia and other countries (Pirmohamed et al 2004, Runciman et al 2003).

Although ADRs also occur with CMs, relatively few reports have been collected through spontaneous post-marketing surveillance systems. The most extensive database of ADRs to herbal medicines is held by the Uppsala Monitoring Centre, which is the coordinating centre for the WHO Programme for International Drug Monitoring (see www.who-umc.org). It receives data from national centres in 72 countries and, over the past 20 years, 11,716 case reports of suspected herbal ADR have been collected. The most commonly reported non-critical effects were (from higher to lower incidence): pruritis, urticaria, rash, erythematous rash, nausea, vomiting, diarrhoea, fever, abdominal pain and dyspnoea. The most common critical effects were: facial oedema, hepatitis, angio-oedema, thrombocytopenia, hypertension, chest pain, convulsions, purpurea, dermatitis and death.

In Australia, the ADRAC database holds reports of suspected ADRs. From 1 November 1972 to 19 April 2005, it has only 1112 reports related solely to CMs. This is reassuring, when one considers that in 2004 approximately 52% of the population were identified as users of at least one non-medically prescribed CM product in the previous 12 months (MacLennan

TABLE 7.4 Examples of Current Databases and Textbooks Reporting on the Purported Ginkgo–Warfarin Interaction

Resource	Interaction information	Comments
MIMS on CD	'Warfarin interacts with a wide range of complementary medicines, including vitamin and herbal preparations, e.g. Gingko biloba … have confirmed or potential interactions with warfarin.'	Accessed 10 July 2008 Ginkgo spelt incorrectly Insufficient information provided
eAMH (Australian Medicines Handbook)	No interaction information	Accessed 10 July 2008 Last updated Jan 2008
AltMedDex (Thomson Reuters 2008)	'Concomitant use of ginkgo and anticoagulants may increase the risk of bleeding complications. '*Adverse effect:* increased risk of bleeding '*Clinical management:* Avoid concomitant use of ginkgo and anticoagulants. '*Severity:* major '*Onset:* delayed '*Documentation:* fair '*Probable mechanism:* Ginkgolide B may inhibit platelet activating factor (PAF)-induced platelet aggregation'	Accessed 10 July 2008 Information does not reflect current evidence base.
The desktop guide to complementary and alternative medicine (Ernst et al 2006)	'Potentiation of anticoagulants is often mentioned, but a systematic review of the evidence refuted the notion.'	Published 2006 Succinct and evidence based
Herbs and natural supplements – an evidence based guide (Braun & Cohen 2007)	'Theoretically, ginkgo may increase bleeding risk when used together with warfarin; however, two randomised double-blind studies have found that *Ginkgo biloba* does not affect the pharmacokinetics or pharmacodynamics, INR or clinical effects of warfarin … and two clinical trials have not found evidence of significant effects on bleeding… Due to the potential seriousness of such an interaction, caution is still advised.'	Last updated 2006 Evidence based
The ABC clinical guide to herbs (Blumenthal 2003)	'Interaction with drugs inhibiting blood coagulation cannot be excluded.' Several case reports of bleeding reported, followed by RCTs showing no evidence of interaction with warfarin or aspirin.	Published 2003 Evidence based

et al 2006). The relatively small number of case reports can be interpreted as indicative of the comparative safety of CMs and the effectiveness of pre-market checks; however, the impact of under-reporting should not be dismissed.

Research on under-reporting of serious ADRs in the USA and Canada suggests that formal reporting rates may be as low as 1.5% of total ADRs (Miller et al 2006). In the specific case of CMs, CAM practitioners and retail staff may not report such events because:

- they are unaware of ADR schemes
- they are not qualified or trained to consider the possibility of ADRs
- they are not motivated to report any ADR that comes to their notice.

In addition, herbal medicine consumers may not be motivated to report ADRs to their physician, as one British study suggests (Barnes et al 1998), or they may not consider the possibility that their symptoms may be related to the CM products they use.

CASE REPORTS AND POST-MARKETING SURVEILLANCE SYSTEMS

Given that current knowledge about CMs is incomplete and that controlled studies are often lacking for CAM, well-documented case reports can serve as a critical early warning system until further research is undertaken, whereas poorly documented case reports can be misleading. Unfortunately, reports of ADRs with herbal medicines often cause some controversy and contain incomplete data; for example, one systematic review, which assessed information from four electronic databases, located 108 cases of suspected medicine–herb interactions. Of these, 68.5% were classified as 'unable to be evaluated' and only 13% were described as 'well-documented' (Fugh-Berman & Ernst 2001). Table 7.5 lists the elements that should be included in a report of an adverse reaction.

Besides improving the quality of reporting, the ideal would be to chemically analyse the product to authenticate the ingredients and

TABLE 7.5 Important Components of an Adverse Reaction Report

Patient demographics: male/female, age, social history if relevant
Suspected product details: formula as stated on label, batch number, expiry date and Aust L or Aust R number
Details of the person making the report
Manufacturer's details
Relevant medical history
Other medicines and treatments being used (including other complementary medicines)
Dose used, duration of use and administration form
Date and time of onset
Adverse effects: description of signs and symptoms
Outcome of event
Information regarding re-challenge, if applicable Presence of confounding variables: e.g. additives

make sure that quality control issues are not involved. This is particularly important when the implicated product has not been manufactured under a strict GMP code.

Much of the information obtained from the current spontaneous post-marketing surveillance systems about CM safety is of limited value, as it does not provide an estimate of the incidence of adverse reactions. Without understanding the level of incidence, case reports can easily be interpreted as cause for alarm or alternatively dismissed as irrelevant. Additionally, authorities discourage reporting of less severe ADRs, so many mild-to-moderate side effects remain undetected and are a hidden source of patient morbidity.

Post-marketing surveillance systems aim to detect trends in ADR and become useful when a large number of reports relating to a specific medicine are received. When evidence gathers to suggest a significant problem, the TGA may issue an alert on its website, impose new conditions on the product's listing or registration, suspend or cancel listing or registration, impose new manufacturing conditions and, if considered sufficiently serious, issue a mandatory product recall. Alerts in recent years have included warnings about drug interactions with St John's wort (*Hypericum perforatum*), suspected hepatotoxicity with products containing kava kava and renal toxicity with Chinese herbal medicines containing the herb *Aristolochia*. The Complementary Medicines Evaluation Committee (CMEC) advises the TGA on matters regarding CMs and is made up of people considered expert in this area.

The two cases involving black cohosh and kava kava provide recent examples. On 9 February 2006 the TGA announced that it had reviewed local and international reports and concluded that, although some reports were confounded by the presence of multiple ingredients, there was sufficient evidence of a causal relationship between black cohosh and serious hepatitis. As a result, the TGA decided that products containing black cohosh must be accompanied by a warning statement on the label:

'Warning: black cohosh may harm the liver in some individuals. Use under the supervision of a healthcare professional.'

A few years earlier, local and international reports suggesting a link between kava kava and hepatotoxicity were received by the TGA. This eventually led to a voluntary recall of kava-containing products by the CM industry and a recommendation in August 2002 that people discontinue use of these products.

The conclusion and recommendations of the TGA have not always been met with agreement from CAM practitioners. In both of the above instances, the initial warnings were considered overly cautious, as the case reports tended to be of poor quality. Based on the high consumption of these medicines and the relative lack of ADRs reported in clinical trials and collected by surveillance systems in general, calls were made for further investigation.

Largely in response to these issues, the Kava Evaluation Group was established in January 2003 to review the accumulating safety data, and by August 2003 CMEC had recommended to the TGA that certain forms of kava could be considered safe. The TGA accepted these recommendations and amended the regulations accordingly. Currently, there is a limit of 125 mg kavalactones allowable per tablet or capsule, and no product must provide more than 250 mg kavalactones in the recommended daily dose.

With regard to the safety of black cohosh, a wait-and-see approach has been adopted.

FACTORS THAT MAKE AN ADR MORE LIKELY

Although little investigation has been conducted into what factors influence the likelihood of ADRs with CMs, it can be assumed that most factors that increase the risk of ADRs with pharmaceutical medicine will also apply to CMs. These factors can be grouped as patient-related or therapeutic.

Patient-related factors

- Older age. Declining liver and kidney function as a result of ageing can increase sensitivity to both therapeutic and adverse effects. During times of ill health, the elderly can experience a further loss of homeostatic reserve, once again increasing sensitivity to the effects of medicines and interactions (Atkinson et al 2001).
- Females appear to be more susceptible to ADRs.
- Concurrent disease, acute and/or severe.
- History of atopic disease.
- Confusion.
- Genetic factors: for example, variations in liver enzymes.
- Reduced renal or hepatic function. Altered metabolism or excretion of a medicine can increase the risk of toxicity
- Self-medication. Prudent self-care can offer numerous benefits to the individual, society and the healthcare system if there is access to quality services, products and information. However, when people at higher risk of adverse effects self-medicate with OTC medicines, it can be potentially harmful. Additionally, interactions that do not produce a clinically obvious change, such as elevation in blood pressure, serum cholesterol or warfarin INR, can remain undetected and uncorrected unless professional advice is sought.
- Use of multiple healthcare practitioners. This is of concern when practitioners fail to communicate effectively with one another to ensure that interactions are avoided and identified.

Therapeutic factors

- Dose. Most ADRs are dose related, with higher doses increasing risk.
- Route of administration (e.g. topical application) can cause delayed hypersensitivity.
- Prolonged and/or frequent therapy.
- Medicines not manufactured under a code of good manufacturing practice (GMP) have an increased risk of extrinsic effects.
- Use of concurrent high-risk medicines; for example, those with a narrow therapeutic index (NTI) such as warfarin, digoxin, lithium, cyclosporin, phenytoin, barbiturates, theophylline, many HIV medicines (e.g. saquinavir), antineoplastic agents (e.g. methotrexate) and anti-arrhythmic agents (e.g. quinidine). These medicines are particularly sensitive to pharmacokinetic alterations in which small changes to blood concentrations can cause a clinically significant change to drug activity. Depending on whether drug concentrations are reduced or increased, there is the potential to cause a loss of efficacy or induce toxic effects, respectively.
- Polypharmacy. This is of particular concern in the elderly, who may have chronic diseases and are known to use more medicines than any other age group, increasing the risk of interactions. Additionally, in many serious diseases such as cancer and HIV, multidrug treatment is the standard of care.
- Use of medicines known to induce or inhibit cytochrome (CYP) enzymes, particularly CYP 3A4, which is responsible for the metabolism of many common pharmaceutical medicines.

STRATEGIES FOR PREVENTING AND LIMITING ADRs

Many countries are trying to cope with the growing problem of ADRs and their associated morbidity and mortality. Currently in Australia and New Zealand there are many structures and initiatives in place, such as regulatory agencies, the CMEC, 'quality use of medicines' organisations and information providers, safety and quality organisations and professional bodies; however, it is ultimately the practitioner and the patient who play the definitive roles.

Strategies for clinicians

- Encourage open and honest communication — between patient, carer and practitioner, and between fellow practitioners about treatments prescribed. One way of achieving this is for CM practitioners to label all dispensed herbal medicines with the botanical names of the herbs included in the product, together with suggested dosage, date of manufacture and practitioner's contact details.
- Take a careful medical and medicines history, including previous allergies and adverse effects.
- Consider non-medicinal treatments.
- Avoid polypharmacy and complicated treatment regimens.
- Become familiar with the potential safety issues associated with a medicine to avoid unnecessarily inducing an ADR or misdiagnosing one as a symptom of a new disease. An important adjunct to this is having access to reliable medical and CM information,

and having a network of experts or informed colleagues to consult. Computer-generated prescriptions and decision-support systems are frequently advocated as possible solutions and can be useful if their information is accurate and updated frequently.
- Regularly review therapeutic goals and medicines being used. This provides an opportunity to promote patient compliance and ensure that the appropriate medicines are being taken safely.
- When problems do arise, practitioners need to be aware of their professional responsibility to report a suspected ADR to one of the following:
  - Adverse Drug Reactions Advisory Committee (Reporting is confidential, open to everyone and is now possible online at www.tga.gov.au.)
  - Relevant herbal and natural medicine associations such as the National Herbalists Association of Australia, (www.nhaa.org.au)
  - Relevant manufacturer (Manufacturers keep their own records and are formally obliged to inform the TGA Prescriber, if applicable.)

Strategies for patients

Patients also play an important role in promoting a beneficial and harm-free outcome. They should ensure that they understand the benefits and potential risks associated with their treatment and be confident that they know how to take/use it appropriately. The Australian Commission on Safety and Quality in Health Care has produced a patient information booklet entitled *10 tips for safer health care* (ACSQHC 2006) to encourage patients to become more active in their own healthcare while in hospital. Many of the steps outlined in the booklet are relevant to people taking CMs in the community or in hospital.

Below is a summary of recommendations for patients choosing to use or currently using CM, adapted from *10 tips for safer health care*.
- Choose a suitably experienced and qualified CM practitioner or ask for referral from a trusted medical practitioner, pharmacist or other source.
- Become an active member of your own healthcare team. Help clinicians reach an accurate diagnosis, discuss appropriate management strategies, ensure treatment is administered and adhered to, identify side effects quickly and take appropriate action.
- Tell all healthcare practitioners about all the medicines being used (complementary and conventional). This includes telling doctors about complementary medicines and telling naturopaths and herbalists about pharmaceutical medicines.
- Make sure information given by the healthcare practitioner about the condition and the treatment options available is understood. In the case of lengthy explanations or recommendations, ask the practitioner to provide written information that can be taken home.
- Ask questions when you need more information because you are uncertain or the information provided is unclear.
- Be motivated to learn about the health condition being addressed, treatments being used and ways to improve wellbeing, by referring to reliable information sources.

THE RATIONAL USE OF HERBAL AND NATURAL MEDICINES

Overall, when manufactured, prescribed and used appropriately, the safety of OTC CMs is high. Serious adverse effects and dangerous interactions are rare, particularly in comparison with the thousands of reports attributed to pharmaceutical medicines. Even so, the assessment of likely adverse reactions or interactions should remain integral to patient management.

Currently, there are few large-scale clinical studies confirming and clarifying the clinical significance of most suspected adverse reactions and interactions associated with CMs, and much remains unknown. It is important to recognise that the information presented in this book requires individual interpretation, because the clinical effects of any medicine or any potential interaction, no matter how well documented, will not occur consistently in each patient, each time or to the same degree of intensity.

Ultimately, the ideal in clinical practice is to combine knowledge about the medicine and the disease, experience of both, and information about the patient and the individual's circumstance in order to make wise treatment choices (Table 7.6, p 92). This requires the application of current knowledge, as well as good observational skills, open communication and clinical experience to reduce the risk of adverse reactions and maximise successful outcomes.

TABLE 7.6 Factors to Consider in the Rational Use of Complementary Medicines

Factors to consider	Rationale
Products that are not produced under a code of GMP **should not be used.**	The quality of the product cannot be guaranteed.
Know the benefits, risks, potential adverse reactions and interactions and seek out reliable information. Additional training and/or access to accurate and updated information is important.	More than half the population use CMs and there is no sign of their popularity abating. Some CMs have proven benefits and offer cost-effective treatment options; however, safety issues also exist. Marketing/sales and company information is not sufficient, and education in the area of CM efficacy and safety may be limited.
Do not rely on label claims alone.	Although manufacturers must hold the evidence to support the claims made on a product label, often the label claims do not provide enough information to make an informed judgment.
Do not rely on label dose recommendations alone.	Some manufacturers state the lowest effective dose on the label to ensure that a patient's general requirements will be met; however, in practice, practitioners should prescribe a dose to meet the individual's needs, which may be higher than label doses, yet still be within safe limits.
Take care when high-risk medicines are involved.	In combination with drugs that have a narrow therapeutic index and many anticancer and HIV medicines, screen for interactions. In the case of herbal medicines, any product containing St John's wort (*Hypericum perforatum*) should be considered higher risk. Screen for interactions.
Take care with people considered to be at higher risk of adverse reactions or in 'at risk' circumstances.	Older age; reduced renal or liver function; acute or severe disease; polypharmacy; history of atopy and/or confusion; when drugs with a narrow therapeutic index are involved; during pregnancy or lactation; in children; before major surgery
Ensure that all health professionals involved in a patient's care are aware of CM use.	Effective communication will foster appropriate and safe use.
Do not assume all healthcare professionals have the knowledge to monitor safe use.	Few medical practitioners have had formal training in the safety issues of CM, and not all health practitioners have ready access to evidence-based safety data.
Know the manufacturer and supplier details.	If in doubt about a product, call the manufacturer or supplier for more information.
Know the prescriber's details (if relevant).	The original prescriber may have valuable information about the patient and the medicine, which may assist informed decision making.
Medicines should be stored appropriately.	Appropriate storage will depend on the patient's circumstance (e.g. at home, in hospital or in a hospice), level of vigilance and the type of medicine used.

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CHAPTER 8
INTERACTIONS WITH HERBAL AND NATURAL MEDICINES

A pharmacological interaction is said to occur when the response to one medicine varies from what is usually predicted because another substance has altered the response. Usually the term 'interaction' has a negative connotation when referring to medicines, because it can lead to drug toxicity or a loss of drug effect, and it may be difficult to predict. However, interactions can also benefit the patient by improving outcomes, reducing side effects or reducing costs. In order for healthcare professionals to interpret interaction data and avoid or beneficially manipulate an interaction, or deal with an adverse effect due to an interaction, it is essential to have an understanding of the mechanisms involved.

Although thousands of drug interactions are studied each year, there has been relatively little scientific investigation into interactions with herbal and natural medicines. Research conducted with pharmaceutical medicines can provide some theoretical insights into the mechanisms of drug–herb interactions, but predicting clinical significance is difficult. Unlike conventional medicines, herbs and food-based supplements contain a complex mixture of bioactive chemicals, some of which may contribute to the overall therapeutic effect of the substances. The chemical composition is also variable and depends on factors such as the plant part used, seasonality, growing and harvesting conditions, and extraction and manufacturing processes. Furthermore, some plant constituents have poor oral bioavailability, so in vitro screening for interactions will produce misleading results.

Evidence from controlled human studies has been increasing steadily in recent years; however, most information is still derived from in vitro and animal experiments. This approach is not without its limitations, as using evidence to predict what will happen in humans from studies not conducted in humans is bound to have inaccuracies and therefore must be interpreted cautiously.

It must be mentioned that even when evidence from a controlled human study is available, predicting the likelihood and severity of a real-life interaction in a specific patient is still difficult and prone to error. Ultimately, the clinical importance of a herb–drug interaction depends on factors that relate to the medicines involved and the patients themselves. The chief medicinal factors will be dose, duration and frequency of use, and administration route. Individual patient factors include age, gender, food intake, gastric and urinary pH, current state of health, preexisting disease and genetic polymorphism.

INTERACTION MECHANISMS

When one considers the great variation in physical properties and pharmacological effects of the numerous substances used as medicines, together with the variable nature of herbal medicines, it is apparent that a virtually endless number of interactions are possible. It is generally accepted, however, that there are two major interaction mechanisms, namely pharmacokinetic and pharmacodynamic interactions. A third minor category of physicochemical or pharmaceutical interactions also exists. Regardless of the mechanism involved, there can be three possible outcomes from an interaction:

- increased therapeutic or adverse effects (additive or synergistic)
- decreased therapeutic or adverse effects (additive or synergistic)
- a unique response that does not occur when either agent is used alone.

PHARMACOKINETIC INTERACTIONS

Pharmacokinetics refers to the quantitative analysis of the absorption, distribution, metabolism and excretion of a medicine. Pharmacokinetic interactions occur when there is an alteration to any of these four processes, causing a change in the amount and persistence of available drug at receptor sites or target tissues. As a result, a change in the magnitude of effect or the duration of effect can occur without a change in the type of effect. Interactions of this type may have multiple mechanisms, making clinical predictions difficult. Additionally, there are many patient factors that influence the pharmacokinetics of a drug, such as age, liver and renal function, degree of physiological stress, and the presence of other diseases such as hyperthyroidism.

Factors affecting absorption

Drug absorption is determined by the physicochemical properties of a drug, as well as by its formulation and route of administration. Because most herbal and nutritional medicines are administered orally, as tablets, capsules, teas and tinctures, this discussion will focus on interactions associated with these dose forms.

Most absorption of orally administered medicines occurs in the small intestine, which has a larger surface area than the stomach and greater membrane permeability. If a slow-release dosage form is taken and it continues to release drug for more than 6 hours, then absorption will also occur in the large intestine. The absorption of oral dose forms is influenced by differences in pH along the gastrointestinal tract, surface area per luminal volume, blood perfusion, the presence of bile and mucus, and the nature of epithelial membranes. Changes to gastrointestinal flora, transport systems, chelation and ion exchange also influence absorption.

Interactions at this level can alter the rate of absorption and/or extent of absorption of a medicine.

Changes in relative rate of absorption

Although a medicine may eventually be fully absorbed, a significantly slowed absorption rate may mean that it never reaches effective serum levels, or that an unwanted 'sustained release' effect causes prolonged activity or a delay in prompt relief. In some clinical situations, decreased rates of absorption are of no concern; however, in others it may be important. Generally, a decreased rate of absorption is less important for medicines that are given in multiple-dose regimens to achieve a steady state serum level than for those that are given as single doses or are required to produce a rapid effect (e.g. analgesics).

Changes in extent of absorption

Altering the extent of absorption may also have significant consequences. Increasing the amount of medicine absorbed may produce higher plasma levels and a higher risk of adverse reactions or toxicity. Alternatively, reducing the amount of medicine absorbed may result in reduced efficacy or therapeutic failure. This is particularly of concern for medicines with a narrow therapeutic index, such as warfarin and digoxin.

Mucilaginous herbs

Although little research has been conducted to determine the effects of herbal medicines on the absorption of other medicines, one double-blind study found that guar gum slowed the absorption rate of digoxin, but did not alter the extent of absorption, whereas penicillin absorption was both slowed and reduced (Huupponen et al 1984). This brings into question the effects of other gums and highly mucilaginous herbal medicines, such as *Ulmus fulvus* (slippery elm), *Althea officinalis* (marshmallow) and *Plantago ovata* (psyllium). Poorly lipid soluble, the mucilaginous content forms an additional physical barrier to absorption, but whether this will have a clinically significant effect on rate and/or extent of absorption of other medicines is uncertain and remains to be tested.

Nutrients

More research has been conducted on the way nutrients interact and alter the absorption of pharmaceutical medicines than with herbal medicines. The interactions between iron and many minerals provide a useful example. Aluminium, calcium bicarbonate or magnesium trisilicate taken in antacid preparations are known to reduce the extent of iron absorption owing to an alteration in gastric pH. This type of interaction is easily avoided by separating the intake of iron by at least 2 hours from the last dose of antacid.

Intrinsic drug transporters

Until recently, when an orally administered medicine exhibited poor absorption, it was generally assumed that this was because of either

physicochemical problems or significant first-pass hepatic metabolism. Recently, it has been recognised that for many medicines poor oral bioavailability could be related to the influence of transporter proteins (Benet & Cummins 2001). Transporter proteins are associated with the transfer of some medicines from the intestinal lumen, through the biological barrier of the intestinal mucosa, into the systemic circulation and back again. Transporters fall into two main categories: carriers and pumps. Carriers are involved in three types of transport processes: facilitated diffusion, co-transport and counter-transport. Pumps are distinguished from carriers by the linkage of transport to an external source of energy. Examples of transporters in the intestine are P-glycoprotein (P-gp), members of the multi-drug-resistance-associated protein family (breast-cancer resistance protein, organic cation and anion transporters), and members of the organic anion polypeptide family (Wagner et al 2001). Of these, P-gp is the most studied (see *Clinical note*).

Herbal and natural medicines affecting P-gp

The influence of herbal and natural medicines on P-gp expression has only recently been considered, so much is still unknown and speculative. To date, most research has centred on St John's wort, although clinical testing with other herbs has now gained momentum: every few months more studies investigating the likelihood and clinical significance of proposed interactions are published.

In 1999, clinical testing found that St John's wort significantly reduces serum levels of digoxin after 10 days' co-administration (Johne et al 1999). The suspected mechanism of interaction was chiefly liver enzyme induction; however, the magnitude of effect seen in this study, and in others, suggested that P-gp induction was involved (Hennessy et al 2002). More recently, several clinical tests have confirmed that St John's wort has significant P-gp induction effects. One study found up to a 4.2-fold increase in P-gp expression compared with a placebo after 16 days' administration.

Clinical note — P-glycoprotein: an important drug transporter

P-glycoprotein was first studied in the context of cancer research, where its overexpression in tumour cells is associated with multi-drug resistance (Jodoin et al 2002). In cancer cells, P-gp is one of the transporters responsible for actively expelling chemotherapeutic drugs from cells, thereby decreasing intracellular concentrations and thus drug efficacy. As a result, identification of those substances that reduce P-gp expression and can be administered safely with chemotherapeutic agents is being investigated.

P-gp is found on the surface of hepatocytes, and epithelial cells of the renal tubules, the intestine, placenta and capillaries in the brain (Lin 2003). It plays an important role in the processes of absorption, distribution, metabolism and excretion of medicines. P-gp has a counter-transport activity, meaning it can transport medicines from the blood back into the gastrointestinal tract, thereby reducing bioavailability.

In humans, P-gp demonstrates genetic polymorphism, which may partly account for the inter-individual variability seen in drug absorption. One study conducted in 25 volunteers supports this idea and found that a greater than eightfold difference in expression of intestinal P-gp is possible (Lown et al 1997).

The expression of P-gp can be altered by a number of factors, such as everyday foods, herbs and pharmaceutical medicines. In the case of P-gp inhibition, there will be an increase in absorption, systemic exposure and tissue distribution of medicines that are P-gp substrates, whereas P-gp induction produces the opposite effect.

Interactions with substances that inhibit P-gp are of great interest, as they can potentially enhance the absorption of important medicines that are generally poorly absorbed, such as chemotherapeutic medicines. Alternatively, P-gp inhibition may theoretically increase the incidence of side effects or the toxicity of some medicines, producing unwanted effects.

Some important P-gp substrates are:

Berberine	Methotrexate
Colchicine	Morphine
Cortisol	Nifedipine
Cyclosporin	Progesterone
Digoxin	Protease-inhibitors
Erythromycin	Taxol
Indinavir	Tamoxifen
Loperamide	*Vinca* alkaloids

Similar results were seen in another study in which 14 days' administration of St John's wort resulted in a 1.4-fold increased expression of duodenal P-gp (Durr et al 2000). Induction of P-gp is attributed to pregnane X receptor activation by the hyperforin constituent (Lin 2003). Low hyperforin products are therefore less likely to induce P-gp.

St John's wort is not the only natural substance found to influence P-gp. In vitro studies suggest that rosemary extract may have the opposite effect, inhibiting P-gp. Treating multi-drug-resistant mammary tumour cells with rosemary extract produced an increase in intracellular concentrations of doxorubicin and vinblastine (both P-gp substrates) (Plouzek et al 1999). The same effects were not seen in cells that lack P-gp expression, suggesting that rosemary extract inhibits P-gp activity. The isoflavone genistein has also been investigated, with some results suggesting inhibition of P-gp-mediated drug transport (Castro & Altenberg 1997). Other studies have found that different polyphenols, such as green tea polyphenols, resveratrol (a polyphenol from red wine), curcumin, caffeine, theanine and methoxyflavones from orange, may inhibit drug transport via P-gp (Jodoin et al 2002).

Grapefruit juice is well known to interact with a number of medicines, so it is not surprising that it has also been investigated for effects on P-gp. Currently, evidence is conflicting, as several studies have found that components in grapefruit juice inhibit P-gp (Eagling et al 1999, Ohnishi et al 2000, Soldner et al 1999, Spahn-Langguth & Langguth 2001), whereas a randomised, crossover clinical study found no significant effects (Becquemont et al 2001). A more recent in vitro study produced similar results with 5% normal concentration of grapefruit, orange and apple juices; however, inhibition of other transporter proteins was observed (Dresser et al 2002).

New research suggests that quercetin inhibits P-gp expression (Choi & Li 2005, Chung et al 2005, Kitagawa et al 2005, Wang et al 2004). Studies with experimental models have demonstrated that pretreatment with quercetin increases the bioavailability of the calcium-channel blocker, diltiazem (Choi & Li 2005), and of digoxin (Wang et al 2004). Intriguingly, one in vivo study found quercetin significantly decreased the oral bioavailability of cyclosporin, which is the opposite to what would be expected, suggesting that other mechanisms may also be involved (Hsiu et al 2002).

Although in vitro studies have also identified an inhibitory effect on P-gp for silymarin, the active constituent group in St Mary's thistle (Chung et al 2005, Zhang & Morris 2003), recent clinical testing found no significant effect in vivo (Gurley et al 2006).

Table 8.1 (p 98) lists herbal and natural medicines that have suspected or known effects on P-gp, together with the research that gives evidence for these effects.

Factors affecting metabolism

Metabolism can occur before and during absorption, thereby limiting the amount of drug reaching the systemic circulation. In the intestinal lumen, digestive enzymes and bowel flora are capable of causing a wide range of metabolic reactions. The intestinal mucosa is also capable of metabolising drugs, with new research suggesting it is a major metabolic organ for some medicines (Doherty & Charman 2002).

For many medicines, metabolism chiefly occurs in the liver in two apparent phases, known as phase I or functionalisation reactions and phase II or conjugation reactions. Phase I reactions include oxidation, hydroxylation, dealkylation and reduction. Examples of Phase I reactions include conversion of an active drug to an inactive, less active, more active or toxic metabolite, and conversion of an inactive prodrug to an active metabolite. Phase II reactions include glucuronidation, sulfation, acetylation and methylation glutathionation, glycination and other amino acid conjugations (taurine, glutamine, carnitine, arginine), and usually result in the formation of inactive compounds that are water-soluble and easily excreted (Blower et al 2005).

Although there are many enzymes responsible for phase I reactions, the most important enzyme group is the cytochrome P450 system (CYP), which comprises more than 50 enzymes and is responsible for the metabolism of many drugs, nutrients, endogenous substances and environmental toxins.

Cytochromes

Cytochrome P450 is a generic term for a super-family of enzymes (haem containing mono-oxygenases) that have existed throughout nature since the beginning of life more than 3.5 billion years ago (Pirmohamed & Park 2003). The P450s are found chiefly in the liver, but also to a lesser extent in the intestines, kidneys, skin and lungs. These enzymes are

TABLE 8.1 Herbal and Natural Medicines with Suspected or Known Effects on P-Glycoprotein

Herbal/natural medicine	Effect	Evidence
St John's wort	Induction	Clinical studies (Hennessy et al 2002, Johne et al 1999) In vivo and clinical study (Durr et al 2000) In vitro (Perloff et al 2001), also positive for hypericin Case report (Barone et al 2000)
Grapefruit juice	Inhibition	Clinical studies (Di Marco et al 2002, Edwards et al 1999) In vivo (Spahn-Langguth & Langguth 2001, Tian et al 2002) In vitro (Eagling et al 1999, Ohnishi et al 2000, Soldner et al 1999, Takanaga et al 1998)
Grapefruit juice	No effect	Clinical study (Becquemont et al 2001)
Orange and apple juice	Inhibition	Clinical study: Seville orange (Di Marco et al 2002) In vivo: orange (Tian et al 2002) In vitro (Ikegawa et al 2000, Takanaga et al 2000)
Rosemary extract	Inhibition	In vitro (Plouzek et al 1999)
Genistein and diadzein	Inhibition	In vitro (Evans 2000, Castro & Altenberg 1997)
Genistein and diadzein	Possible induction	In vitro (den Boer et al 1998)
Resveratrol	Inhibition	In vitro (Jodoin et al 2002)
Curcumin	Inhibition	In vitro (Anuchapreeda et al 2002, Romiti et al 1998)
Quercetin	Inhibition	In vitro and in vivo (Choi & Li 2005, Chung et al 2005, Kitagawa et al 2005, Scambia et al 1994, Wang et al 2004)
Green tea polyphenols, especially epigallocatechin gallate	Inhibition	In vitro (Jodoin et al 2002, Sadzuka et al 2000)
Piperine (a major component of black pepper)	Inhibition	In vivo (Bhardwaj et al 2002)
St Mary's thistle	Inhibition	In vitro tests (Chung et al 2005, Zhang & Morris 2003)
St Mary's thistle	No effect	Human study (Gurley et al 2006)

responsible for foreign compound metabolism, which evolved about 400–500 million years ago to enable animals to detoxify chemicals in plants. The cytochrome P450 (CYP) enzymes are the most powerful in vivo oxidising agents and are able to catalyse the oxidative biotransformation of a wide range of chemically and biologically unrelated exogenous and endogenous substrates. They are named by a root symbol CYP, followed by a number for family, a letter for subfamily, and another number for the specific gene. For example, CYP3A4 would refer to a specific enzyme from the cytochrome P450 system, family 3, subfamily A and gene 4. Three main CYP families (CYP1, 2, 3) are responsible for metabolism of therapeutic drugs. The different P450 isoforms vary in their abundance within the liver. Of these, the cytochromes CYP2C9, CYP2D6 and CYP3A4 are the most abundant in the human body (Pirmohamed & Park 2003).

The CYP2C sub-family accounts for 15–20% of the total P450 content of the liver, and metabolises approximately 20% of all drugs (Pirmohamed & Park 2003). The main member of this sub-family is CYP2C9, which is responsible for the metabolism of a number of compounds, including warfarin, phenytoin and various NSAIDs. Cytochrome 2D6 is responsible for the metabolism of approximately 25% of therapeutically used drugs, although it accounts for only < 5% of the total P450 content. The CYP3A sub-family accounts for 30% of the total P450 content and is responsible for metabolism of about 50% of therapeutic drugs. Table 8.2 provides examples of common drugs

TABLE 8.2 Selected Drugs that Act as Substrates for CYP Enzymes

CYP enzyme	Drugs
CYP1A2	amitriptyline, caffeine, melatonin, naproxen, paracetamol, tacrine, theophylline, verapamil, R-warfarin
CYP2B6	amitriptyline, diazepam, methadone, midazolam, tamoxifen, temazepam, testosterone
CYP2C9	amitriptyline, celecoxib, diclofenac, fluoxetine, ibuprofen, tamoxifen, S-warfarin
CYP2C19	amitriptyline, imipramine, indomethacin, omeprazole, progesterone, propranolol, R-warfarin
CYP2D6	amitriptyline, beta blockers, codeine, fluoxetine, flecainide, haloperidol, nicotine, ondansetron, paroxetine, sertraline, tamoxifen, tramadol
CYP3A4	alprazolam, caffeine, codeine, cyclosporin, erythromycin, HIV antivirals (e.g. indinavir), lovastatin, midazolam, oestradiol, ondansetron, progesterone, simvastatin, tamoxifen, taxol, testosterone

and the cytochromes chiefly responsible for their metabolism. For a more complete list that is frequently updated, see Flockhart 2007.

The expression and activity of many CYP isoenzymes vary enormously between individuals. Part of the inter-individual variability is environmentally determined by the concomitant intake of drugs and foodstuffs that cause induction and inhibition of the different P450 isoforms. P450 gene polymorphism may also influence expression and activity of CYP enzymes, as this can lead to:

- abolished activity of a CYP enzyme (e.g. CYP2C9, CYP2C19 and CYP2D6 can be genetically absent in some livers [USFDA 2006])
- reduced activity
- altered activity
- increased activity where there is gene duplication.

For example, one study identified that 30% of Ethiopians had multiple copies of the 2D6 gene (up to 13), resulting in ultra-rapid metabolism of CYP2D6 substrates (Aklillu et al 1996). As a result, standard doses of CYP2D6 substrates (e.g. beta-blockers, some opioids and tricyclic antidepressants) will not produce anticipated or adequate responses, and higher drug doses are necessary to produce therapeutic effects. It has also been estimated that 7% of Caucasians lack CYP2D6. These individuals will not experience the anticipated therapeutic effects of prodrugs that are CYP2D6 substrates, such as codeine, and will appear more sensitive to the side effects of CYP2D6 substrates (e.g. beta-blockers, some opioids and tricyclic antidepressants) (USFDA 2006).

Another example is the polymorphic distribution of CYP2C9, which is absent in 1% of Caucasians. More than 100 currently used drugs are known substrates of CYP2C9, corresponding to approximately 10–20% of commonly prescribed drugs. Of note, CYP2C9 is chiefly responsible for the metabolism of NSAIDs and COX-2 specific inhibitors (e.g. celecoxib).

Many other factors affect CYP activity, such as the ingestion of foreign compounds (e.g. environmental contaminants) or the ingestion of certain constituents found in food, beverages and medicines.

Because of overlapping substrates, many drug interactions involve both P-gp and CYP3A4.

Enzyme inhibition

Competitive CYP inhibition is dose-dependent and occurs when inhibitors compete with other substances for a particular enzyme. Non-competitive inhibition is also possible and occurs when a substance either destroys or binds irreversibly to a CYP enzyme. In both instances, serum levels of those drugs chiefly metabolised by the affected enzyme will become elevated and the inhibition process is rapid. This is of particular concern with medicines that have a narrow therapeutic index, as very small changes in dose or blood levels can produce significant changes in activity. In the case of enzyme inhibition, raised blood levels can lead to increased side effects and toxicity.

Although inhibition of a CYP enzyme is generally regarded as raising the serum levels of an active drug, this is not always the case. If the drug involved is a prodrug, then it is inactive in its administered form and must be converted to its active form, usually via metabolic processes. If metabolism is slowed, then

the production of active metabolites will also be slowed. An example is codeine, which is primarily metabolised by CYP2D6 into its active analgesic metabolite morphine; therefore, CYP2D6 inhibition has the potential to slow or reduce its analgesic activity.

Inhibitors do not all have the same strength and can be classified as strong, moderate or weak, depending on their effect on drug clearance compared to normal values. For example, Flockhart describes a strong inhibitor as one that causes more than 80% decrease in clearance, a moderate inhibitor as one that causes a 50–80% decrease in drug clearance, and a weak inhibitor as one that causes a 20–50% decrease in drug clearance (Flockhart 2007).

Enzyme inhibition is not always harmful and has been manipulated to raise serum drug levels without the need to increase the dose administered. The result has obvious cost advantages when extremely expensive drugs are involved and has been used in some hospitals for medicines such as cyclosporin.

To date, the most studied natural substance capable of significantly inhibiting CYP enzymes is grapefruit. The finding that grapefruit juice markedly increases the bioavailability of some orally administered medicines was based on an unexpected observation from an interaction study between the calcium-channel antagonist felodipine and ethanol. In the study, grapefruit juice was used to mask the taste of ethanol, but actually affected the results by reducing CYP3A4 by 62% and significantly raising felodipine levels (Bailey et al 1998). Since then, the constituents of grapefruit juice have been extensively studied and found to affect the transport and metabolism of many other medicines (Eagling et al 1999, Kane & Lipsky 2000).

Increasingly, research is being conducted to determine whether other commonly used herbal medicines have an affect on CYP activity in vivo. For example, one research group in the United States screened *Citrus aurantium*, *Echinacea purpurea*, milk thistle (*Silybum marianum*), and saw palmetto (*Serenoa repens*) extracts for effects on CYP1A2, CYP2D6, CYP2E1 and CYP3A4 activity in healthy subjects (Gurley et al 2004). Of the four herbs, only *E. purpurea* was found to have any effect on the CYP enzymes tested, with a minor influence on CYP1A2 and CYP3A4. Using the same method, extracts of the herbs goldenseal (*Hydrastis canadensis*), black cohosh (*Cimicifugaracemosa*), kava kava (*Piper methysticum*) and valerian (*Valeriana officinalis*) were tested for effects on CYP1A2, CYP2D6, CYP2E1 or CYP3A4/5 activity (Gurley et al 2005). Goldenseal strongly inhibited CYP2D6 and CYP3A4/5 activity in vivo, whereas kava kava inhibited CYP2E1, black cohosh weakly inhibited CYP2D6 and no effect was observed for valerian. In a separate study, testing *Panax ginseng* and *Ginkgo biloba*, no effect was observed on CYP activity; however, garlic oil inhibited CYP2E1 activity by 39% (Gurley et al 2002). There are many other examples to be found in the individual monographs of this book.

Enzyme induction

Alternatively, many different medicines and everyday substances have been found to induce the CYP enzymes (e.g. broccoli, Brussels sprouts, char-grilled meat, high-protein diets, tobacco and alcohol). Research is now identifying a number of herbal medicines that cause CYP induction to various degrees; however, the most studied to date is St John's wort.

Clinical tests have confirmed that long-term administration of St John's wort has significant CYP inducer activity, particularly CYP3A4 (Durr et al 2000, Roby et al 2000, Ruschitzka et al 2000, Wang et al 2001). It appears that the hyperforin component is a potent ligand for the pregnane X receptor, which regulates expression of CYP3A4 mono-oxygenase. In this way, hyperforin increases the availability of CYP3A4, resulting in enzyme induction (Moore et al 2000).

Lack of in vitro — in vivo correlation

It is interesting to observe an apparent lack of in vitro – in vivo correlation with some studies of CYP. For instance, in vitro investigations implicate milk thistle extract and/or silibinin as inhibitors of human CYP3A4, CYP2C9, CYP2D6 and CYP2E1; however, in vivo evidence for CYP-mediated interactions by milk thistle is less compelling (Gurley et al 2004). This may be owing to poor bioavailability of key constituents, large inter-individual differences in absorption of constituents, inter-product variability in the ratios of constituent, poor dissolution of dosage forms or other mechanisms.

Factors affecting excretion

The kidneys are the major organs of excretion, but it also occurs to a lesser extent via other routes such as saliva, sweat, faeces, breast milk

Clinical note — Pharmacogenetics

Pharmacogenetics largely deals with genes encoding drug transporters, drug-metabolising enzymes and drug targets (Ingleman-Sundberg 2004). It is now well established that the polymorphism of metabolising enzymes, and in particular that of cytochromes P450s, has the greatest effect on inter-individual variability of drug response, as evidenced by many studies. These polymorphisms affect the response of individuals to drugs used in the treatment of depression, psychosis, cancer, cardiovascular disorders, ulcer and gastrointestinal disorders, pain and epilepsy, among others. The costs of genotyping are reducing and our knowledge about the benefits of predictive genotyping for more effective and safe drug therapy is increasing. This means that in future predictive genotyping for CYP enzymes will become routine, allowing individualised prescribing to produce better clinical outcomes with less risk of side effects.

and the lungs. If a medicine is chiefly eliminated by one pathway, then alterations to that particular pathway can theoretically have a significant influence on its excretion.

With regard to urinary excretion, factors that alter renal function can interfere with the excretion of medicines and their metabolites. There are three main ways that renal function can be modified (Blower et al 2005):

- altered renal tubular reabsorption by substances that affect urinary pH
- changes in renal tubular secretion by agents that either compete for active secretion or that alter the activity of membrane transporter proteins
- changes in glomerular filtration induced by agents that alter cardiac output.

Alterations to urinary pH are easily achieved with regard to herbal and natural substances; for example, the half-life of an acidic medicine, such as a salicylate, can be increased with acidification of urine — for example, with high doses of ascorbic acid, because less is eliminated. Alternatively, the half-life of a weakly basic drug, such as amphetamine, may be decreased when urine is acidified. Alkalisation of urine produces the opposite effects and can occur with low-protein diets or the ingestion of substances such as potassium citrate.

PHARMACODYNAMIC INTERACTIONS

Pharmacodynamic interactions result when one substance alters the sensitivity or responsiveness of tissues to another. This type of interaction results in additive, synergistic or antagonistic drug effects and is of particular concern when medicines used simultaneously have overlapping toxicities.

In practice, clinicians frequently use additive or synergistic pharmacodynamic interactions to improve clinical outcomes. For example, medical doctors may prescribe a combination of antibiotics against difficult-to-eradicate microorganisms, or several antihypertensive drugs to one patient. Herbalists widely prescribe combinations of herbs with similar actions to strengthen clinical effects, and naturopaths may combine nutritional and herbal supplements in a similar way.

Pharmacodynamic interactions do not always produce wanted results, such as when several medicines with overlapping adverse effects or toxicities are used together, leading to more serious adverse effects. An example is the combined use of an opioid analgesic, which can induce drowsiness, and an antiemetic drug such as metoclopramide, which can also induce drowsiness. Other unwanted effects include potentiating drug activity to a clinically uncomfortable or dangerous level, or reducing activity and therefore the effectiveness of treatment.

Although pharmacodynamic interactions involving herbal and natural medicines and pharmaceutical medicines have not been thoroughly investigated, theoretical predictions are easy to produce. For example, case reports suggest that kava kava may have dopamine receptor antagonist activity and therefore theoretically can interact with dopamine agonists (e.g. L-dopa), opposing their effect (Meseguer et al 2002, Spillane et al 1997). Predicting real-life responses is difficult, because the evidence does not come from a controlled clinical study and individual factors such as dose, administration route and patient health further influence outcomes.

PHYSICOCHEMICAL INTERACTIONS

Physicochemical interactions occur when two substances come into contact and are either physically or chemically incompatible. This

type of interaction can take place during the manufacture or administration of medicines and can affect both the rate and the extent of absorption of one or both medicines. Physicochemical interactions are a well-known concern among medical herbalists and naturopaths who prescribe and dispense their own herbal combinations.

Reduced absorption

Tannins

Herbs with significant tannin content have the potential to be involved in physicochemical interactions with other medicines, both outside and within the body, because they form precipitates with proteins, nitrogenous bases, polysaccharides and some alkaloids and glycosides (Mills 1991). Additionally, tannins will form complexes with metal ions such as iron, inhibiting their absorption (Glahn et al 2002). To avoid this interaction, herbal extracts containing tannins are traditionally not mixed with extracts containing alkaloids (Bone & Mills 2000).

In practice, herbal medicines containing tannins are used both internally and externally. When used internally, it is recommended that they be taken between meals or on an empty stomach to minimise precipitation of dietary proteins and digestive enzymes in the gut (Baxter et al 1997). Additionally, tannins can reduce the absorption of some minerals, so should not be taken at the same time. For example, the absorption of iron is significantly reduced in the presence of tannins, with one study finding amounts as small as 5 mg of tannic acid are able to inhibit iron absorption by 20% and higher levels of 100 mg by 88% (Brune et al 1989).

Tannins are widely found in the plant kingdom, as shown in Table 8.3.

TABLE 8.3 Common Herbs with Significant Tannin Content

Common name	Botanical name
Agrimony	*Agrimony eupatorium*
Bearberry	*Arctostaphylus uva-ursi*
Bistort	*Polygonum bistorta*
Meadowsweet	*Filipendula ulmaria*
Raspberry	*Rubus idaeus*
Rhubarb	*Rheum* spp. root
Spinach	*Chenopodium* spp.
Tea	*Camellia sinensis*
Tormentil	*Potentilla tormentilla*

Chelation

Physicochemical interactions can also occur via a process of chelation, which is the chemical interaction of a metal ion and other substance that results in the formation of a molecular complex in which the metal is firmly bound and isolated. In other words, the metal ion irreversibly binds to a second molecule, leading to reduced activity or inactivation of that metal. A common example is the interaction between iron and various drugs, including tetracycline antibiotics.

A number of compounds found naturally in food have the potential to interact with medicines in this way. For example, oxalic acid found in spinach and rhubarb or phytic acid found in bran can form insoluble complexes with calcium, thereby reducing its absorption.

Increased absorption

Not all physicochemical interactions result in reduced absorption. It is widely accepted that interactions between plant components can enhance clinical effects by increasing the bioavailability of key pharmacologically active constituents.

The results of continuing investigation into the chemistry of St John's wort provide a good example. In vivo studies using hypericin and pseudohypericin found that the solubility of these two active constituents increases by approximately 60% in the presence of natural procyanidins (Butterweck et al 1998). Further research has isolated naturally occurring hyperoside, rutin and quercetin as some of the key components responsible for this interaction.

Although still largely speculative, the interaction between naturally occurring surfactant constituents, such as saponins, and poorly lipid soluble active constituents could feasibly result in increased absorption through a micellisation process. Besides improving oral bioavailability, the interaction could also improve dermal penetration.

Different forms of saponins are widely found in the plant kingdom and are used either internally or externally, depending on the particular herb (Table 8.4).

SYNERGY HERBAL RESEARCH

In practice, herbalists use inter-herbal interactions to produce better outcomes. This practice is much the same as that of medical practitioners employing multi-target drug therapy in the treatment of cancer, hypertension

TABLE 8.4 Common Herbs Containing Saponins	
Common name	**Botanical name**
Astragalus	*Astragalus membranaceus*
Bupleurum	*Bupleurum falcatum*
Horsechestnut	*Aesculus hippocastanum*
Japanese ginseng	*Panax japonicus*
Licorice	*Glycyrrhiza glabra*
Poke root	*Phytolacca decandra*
Soybean	*Glycine max*
Withania	*Withania somnifera*

and antibiotic resistance. Owing to the chemical complexity of herbal medicines, intra-herbal interactions are also being identified that largely explain the therapeutic superiority of many herbal drug extracts over single constituents isolated from the same herbal extracts. Synergistic effects can be produced if the constituents of an extract affect different targets or interact with one another in order to improve the solubility and thereby enhance the bioavailability of one or several substances of an extract. Synergy research in phytomedicine has established itself as a new activity in recent years and focuses on studying intra-herbal and inter-herbal interactions to better understand how therapeutic benefits can be harnessed.

INTERACTION SCREENING TOOLS

Information about interactions is derived from in vitro tests, studies with experimental animal models and, increasingly, clinical studies. Most interactions studies conducted to date have focused on herbal constituents and their effects on cytochrome (CYP) enzymes and, increasingly, P-glycoprotein (P-gp), with few studies investigating effects on drug transport or phase II metabolism.

In vitro tests

Most studies conducted to investigate herb–drug interactions have used in vitro testing of herbal constituents in microsomal systems, supersomes, cytosols, expressed enzymes or cell-culture systems such as transfected cell lines, primary cultures of human hepatocytes and tumour-derived cells. While in vitro models provide a quick screening method for potential herb–drug interactions they do not always correlate with in vivo findings. One problem frequently encountered in the existing in vitro literature is the use of inappropriately high concentrations of single, isolated constituents obtained from commercial sources, and utilisation of these in experiments when only a small fraction of the compound may actually be bioavailable. Many natural products are generally subject to first-pass metabolism and to a much larger extent than conventional pharmaceutical agents, which are in most cases specifically developed to be substantially bioavailable or otherwise formulated as prodrugs. In addition, many are less bioavailable because of their hydrophilic nature or large molecular size (Markowitz et al 2008).

Animal studies

These studies may give important information on herb interactions. Probe substrates/inhibitors can be used to explore the effects of herbs on the activity of specific CYP enzyme in vivo, e.g. caffeine for CYP1A2, tolbutamide for CYP2C9, mephenytoin for CYP2C19, dextromethorphan or debrisoquin for CYP2D6, chlorzoxazone for CYP2E1 and midazolam or erythromycin for CYP3A4. In addition, a cocktail of probe drugs have been used to explore the activities of multiple CYPs in the same experiment. Ultimately, in vivo clinical studies are more reliable than in vitro tests as a means of determining the clinical importance of herb–drug interactions, although these studies can quickly be confounded by the documented variability found in specific constituents between individual botanical products as well as by the choice of probe substrates administered (Markowitz et al 2008).

Relying solely on in vitro or animal model experiments to predict clinically relevant herb–drug interactions is problematic and can provide inaccurate information. The herbs *Ginkgo biloba* and saw palmetto will be used here as examples to illustrate this point.

In vitro and/or tests with animal models have shown both cytochrome induction and inhibition for *Ginkgo biloba* (Shinozuka et al 2002, Ryu & Chung 2003, Ohnishi et al 2003, Kubota et al 2004, Kuo et al 2004, He & Edeki 2004, Gaudineau et al 2004, von Moltke et al 2004, Sugiyama et al 2004a, Sugiyama et al 2004b, Chatterjee et al 2005, Chang et al 2006a, Mohutsky et al 2006a, Zhao et al 2006, Chang et al 2006b). In contrast, four clinical studies have failed to identify a clinically significant effect on a variety of cytochromes. In one clinical study, Gurley et al (2002) demonstrated that *Ginkgo biloba* had no significant effect on CYP1A2, CYP2D6 or CYP3A4 activity. Markowitz et al (2003b) also conducted a

human study and found no significant effects on CYP2D6 or CYP3A4 activity. Two further clinical studies found no significant effect for *Ginkgo biloba* on CYP2C9 activity (Greenblatt et al 2006, Mohutsky et al 2006b).

Saw palmetto showed potent inhibition of CYP3A4, CYP2D6, and CYP2C9 in vitro (Yale & Glurich 2005); however, no significant effect was observed on CYP2D6 or CYP3A4 activity according to a clinical study by Markowitz et al (2003a). Gurley et al (2004) also found no significant effect for saw palmetto on CYP1A2, CYP2D6, CYP2E1 or CYP3A4 activity in healthy subjects.

To add to the complexity of the problem, in some instances researchers have conducted testing with individual herbal components or different forms of a herb and found different effects on CYPs. For example, using animal models Fukao et al (2004) demonstrated that diallyl sulphide (100 micromol/kg) increased cytochrome CYP2E1 activity slightly but significantly (1.6-fold versus control), whereas diallyl disulfide and diallyl trisulfide did not affect CYP2E1 activity or the hepatic total CYP level or CYP1A1/2 activity. The significance of these results in clinical practice is difficult to determine, as the overall effect on CYP activity will depend on the concentrations of these various constituents present in a garlic product. The example also highlights the general difficulty in extrapolating results for one herbal extract to another, as there may be a significant chemical variation between batches of the same herbal product and between different products of the same herb grown and produced by various manufacturers.

Clinical studies

These studies provide the most relevant information; however, they are costly to produce and are mostly conducted with young, healthy males, which may or may not accurately reflect the responses of other populations (e.g. women, the elderly).

Table 8.5 presents a summary of the strengths and limitations relevant to different types of interactions research.

PUTTING THEORY INTO PRACTICE

It is clear that many patients will be taking herbal and natural medicines and pharmaceutical medicines at some stage of their lives. In some instances, use will overlap, so a patient will be taking several medicines at the same time. In order to promote the safe use of all medicines, the following section provides ideas for consideration and discussion, practical tools to aid in reducing the risk of interactions and in detection of adverse reactions, and general recommendations.

INTERACTION MECHANISMS

Predicting the clinical importance of a herb–drug interaction is difficult and largely depends on factors that relate to the medicines administered and the individual patient. Having an understanding of the interaction mechanisms involved is also essential.

Medicine factors

Consider the types of medicines involved, administration route, dosage and duration of use. Drugs with a narrow therapeutic index are of most concern, as minor changes to serum levels can have clinically significant outcomes. Drugs that are administered intravenously will not always be subject to the same concerns as orally ingested drugs. In the case of herbal medicines, some preparations contain multiple CYP or transporter-modulating constituents, with some constituents causing induction and others inhibition. This means the overall outcome will depend on the amount of inducer/inhibitor constituents present, the CYPs or transporters affected and the relative strengths of inducers/inhibitors. Since herbal medicines naturally vary in constituent ratios owing to environmental and process factors, their effects on CYPs and transporters are more difficult to predict than for single-entity drugs.

Individual patient factors

The severity of the interaction is also influenced by factors such as age, gender, preexisting medical conditions and comorbidities, environmental influences and diet. Genetic polymorphism is increasingly becoming recognised as another significant factor altering a patient's risk of experiencing adverse drug reactions. The importance an interaction is given is also related to some extent to the setting in which it occurs. Risk can be minimised or managed when patients openly discuss their use of herbal and pharmaceutical medicines with all their healthcare providers and they are carefully supervised.

Problems and pitfalls interpreting the evidence

Firstly, understanding the basic mechanisms involved is essential, as is keeping in mind the type of evidence that might suggest the possibility

of an interaction. It is important to note the general lack of correlation between in vitro and in vivo tests, and the inaccuracies of extrapolating data from animal models to predict clinical significance in humans. In many cases, interaction studies are absent, so clinicians must use their professional judgment to evaluate what is known about the medicines and the patient, and then the likelihood of a clinically relevant interaction.

A PREDICTIVE ALGORITHM

The METOPIA algorithm provides a framework for healthcare professionals when making rational decisions about the introduction of a second, potentially interacting medicine. In this chapter, it is assumed that a herbal medicine is involved. METOPIA stands for:

Medication and mechanisms

- What types of medicines are involved? High-risk medicines such as those with a narrow therapeutic index require closer monitoring.
- Is an interaction theoretically possible? This needs to be based on a fundamental understanding of the pharmacokinetic parameters and pharmacodynamic effects of the medicines involved.

Evidence available?

- Is there supportive evidence for an anticipated interaction?
- If so, what is the weight of that evidence (theoretical, in vitro, in vivo, case reports or clinical trials)?

If the information gathered so far suggests an interaction is possible, continue with the following steps.

Timing and dose — introducing which, when and for how long?

- When are the medicines being taken — at the same time or are doses separated by several hours? It is particularly important to determine the timing if a physicochemical interaction is anticipated.

TABLE 8.5 Advantages and Limitations of Herb–Drug Interaction Studies

Study type	Advantages	Limitations
In vitro	Provides information about specific mechanisms under controlled conditions. Relatively simple to conduct compared with clinical studies. Inexpensive tests to conduct compared with clinical studies. Relatively quick to conduct.	Does not account for poor bioavailability of the test compound. May use one isolated constituent, whereas herbal extracts contain multiple constituents. Does not account for human genetic polymorphism. May use clinically irrelevant concentration. Metabolites of botanical extracts are poorly characterised for most extracts and may contribute to the net inhibitory or inductive effects observed, which will not be detected with in vitro testing.
In vivo using animal models	Can address some of the issues relating to bioavailability. Can produce quicker results than clinical studies. Can provide information when clinical studies are not able to be conducted.	Species variations make results difficult to interpret. Selection of appropriate dosage can be difficult and very large doses are often used. Does not account for human genetic polymorphism.
Clinical studies	Provide the most relevant information and are the most definitive.	Most studies conducted in healthy male subjects; however, most relevant results are obtained when conducted with the population that will be using the product. Inter-product variability in constituent ratios means tested product may not accurately represent effects of other products. Cannot differentiate between gut and liver effects (e.g. cytochromes). Does not provide information about mechanisms. Are costly and time consuming. May never be done for ethical reasons (e.g. safety studies in pregnancy).

- What is the duration of use? Interaction mechanisms may develop only over several days or weeks (such as CYP induction), or may occur more rapidly.

Outcomes possible

- What is the potential clinical outcome of an interaction — major, minor or neutral? In regard to herbal medicine, this is often speculative.

Practitioner considerations

- Is the practitioner in a position to monitor and manage an interaction should it become significant? In a hospital setting, an interaction is generally considered important if something must be done to relieve patient symptoms or if it will have a significant impact on critical therapy. Practitioners and nursing staff are in an ideal position to monitor for interactions and respond quickly should this be necessary. In a community setting, general practitioners, pharmacists, naturopaths and herbalists are better placed, and adequate patient self-monitoring becomes more important.

Individual considerations

- What are the patient's individual preferences and ability to self-monitor a potential interaction should it arise?

Action required

Having established the criteria so far, five actions are possible:

- *Avoid* — consider an alternative treatment that is unlikely to produce undesirable interaction effects.
- *Avoid unless adequate medical monitoring is possible* — changing the dose and regimen may be required for safe combined use.
- *Caution* — tell patients to be aware that a particular event is possible and to seek advice if they are concerned.
- *Observe* — the practitioner is alert to the possibility of an interaction, even though it is unlikely to have clinical consequences and is likely to be a neutral interaction.
- *Prescribe* — the outcome of the interaction is beneficial and can be used to improve clinical outcomes.

ASSESSING THE LIKELIHOOD OF AN ADVERSE DRUG–HERB INTERACTION

The likelihood that an adverse reaction is responsible for a patient's presenting signs and symptoms should always be considered. If suspicious, then it is essential to take appropriate steps to clarify the likelihood of an adverse reaction.

Patient evaluation

Factors to consider are:

- detailed description of the event — severity of symptoms, signs, onset, duration, frequency
- differential diagnoses (e.g. non-medicinal causes, such as exacerbation of condition, laboratory error or an interaction).

Causality and probability

Determining a cause-and-effect relationship between a medicine and an adverse reaction can be difficult. The degree of certainty that links a medicine to a specific reaction can be classified as definite, probable, possible, conditional or doubtful, and must be assessed in each individual case. Several algorithms exist to help clinicians determine the likelihood of an adverse reaction. Table 8.6 shows the Naranjo algorithm adapted for use as an interaction detection tool (Naranjo et al 1981). The adverse drug reaction possibility classification is based on the total score:

>8	highly probable
4–7	probable
1–3	possible
0	doubtful

NEXT STEPS IF INTERACTION IS LIKELY

Analysis of the medicine

If an interaction involving a herbal or natural medicine is highly likely, then it must be authenticated, botanically verified and analysed for the presence of contaminants. These essential steps will establish whether the interaction is due to an intrinsic property of the medicine itself, and therefore reproducible, or to extrinsic factors such as poor manufacturing processes.

Case reporting

All suspected adverse reactions should be reported to several authorities:

- The local government agency responsible for post-marketing surveillance and collecting adverse drug reaction case reports. In Australia this is the Adverse Drug Reactions Advisory Committee (ADRAC) (Reporting

TABLE 8.6 Assessing the likelihood that an adverse reaction is caused by an Interaction

Question	Yes	No	Don't know	Score
Do previous conclusive reports of this interaction exist?* It is suggested that several resources are examined to determine whether the report is a possible, probable or confirmed interaction.	+1	0	0	
Did the adverse event appear after the suspected medicine/herb/nutrient was co-administered?	+2	–1	0	
Did the adverse reaction improve after the suspected medicine/herb/nutrient was discontinued?	+1	0	0	
Did the adverse reaction reappear when the medicine/herb/nutrient was readministered?	+2	–1	0	
Are there alternative causes (other than the suspected medicine/s) that could produce this reaction?	–1	+2	0	
Was the medicine detected in the blood (or other fluids) at levels known to be toxic or subtherapeutic, when previous levels were within the normal range?	+1	0	0	
Was the reaction more severe when the dose of medicine/herb/nutrient was increased, or less severe when decreased?	+1	0	0	
Has the patient had a similar reaction to the same or similar medicine in any previous exposure, when concomitant complementary medicines were not used?	–2	+1	0	
Was the event confirmed by objective evidence?	+1	0	0	
TOTAL score				

*Although a rechallenge provides important evidence, this is not always appropriate.

is confidential, open to everyone and is now possible online at www.tga.gov.au.)
- Relevant local herbal and natural medicine associations such as the National Herbalists Association of Australia (www.nhaa.org.au)
- Relevant product manufacturer (Manufacturers keep their own records and are obligated to inform the TGA.)
- Prescriber, if applicable.

Chapter 7 provides further practical information about the safe use of CAM and risk factors for adverse events and interactions.

TWO MEDICINES REQUIRING SPECIAL ATTENTION

DIGOXIN

Digoxin is a drug indicated for the treatment of numerous cardiac ailments, such as atrial fibrillation and severe heart failure. It has a positive inotropic effect on both normal and failing hearts, although its primary benefit is mediated by neurohormonal modulation. It has a narrow therapeutic index and therefore minor changes in dose or serum levels can have clinically significant consequences. Digoxin is subject to pharmacokinetic and pharmacodynamic interactions with pharmaceutical, herbal and natural medicines, resulting in possible therapeutic failure or toxicity.

Potassium changes

Potassium states are of special concern with digoxin because hypokalaemia lowers the threshold for drug toxicity. It is well known that pharmaceutical medicines such as thiazide diuretics and corticosteroids have the potential to induce a state of hypokalaemia. There are several herbal medicines that require attention such as *Glycyrrhiza glabra* (licorice), *Paullinia cupana* (guarana) and anthraquinone laxatives (e.g. aloes, buckthorn, cascara and senna). As with potassium-depleting drugs, adequate potassium intake should be recommended and potassium levels monitored together with clinical signs and symptoms.

Alternatively, there are a number of herbal medicines and foods that contain significant amounts of potassium that could increase the threshold for drug efficacy. Some of the common herbs and foods containing greater than 50,000 ppm of potassium include asparagus, beetroot, bok choy, cucumber, lettuce, rhubarb, *Avena sativa* (oats), *Taraxacum officinale* (dandelion) and *Apium graveolens* (celery).

P-gp and changes to metabolism

Digoxin is a substrate for P-gp, therefore serum digoxin levels are altered when P-gp induction or inhibition occurs. It is known that drugs such as verapamil and quinidine, which affect P-gp, can significantly interact with digoxin and in recent years several herbal and natural medicines have also been identified with the potential to alter P-gp activity. Of these, the herb St John's wort has been investigated under controlled clinical conditions and found to decrease the digoxin area-under-the-curve by 25% after 10 days' treatment (Johne et al 1999). Monitoring of plasma digoxin concentration and clinical effects is required when patients commence or cease St John's wort while taking digoxin. As discussed earlier, several other herbs affect P-gp expression and concurrent use should be supervised.

Pharmacodynamic interactions

Pharmacodynamic interactions are theoretically possible when herbs containing naturally occurring cardiac glycoside constituents, such as oleander (*Nerium oleander*), false hellebore (*Adonis autumnalis*) and lily of the valley (*Convallaria majalis*), are ingested at the same time. Although not commonly prescribed for internal use, theoretically these plants may reinforce drug activity and induce symptoms of toxicity. Signs and symptoms of digoxin toxicity include anorexia, nausea, vomiting, diarrhoea, weakness, visual disturbances and ventricular tachycardia.

It has been speculated that the herb hawthorn (*Crataegus oxyacantha*) could potentiate the effects of cardiac glycosides, as both in vitro and in vivo studies indicate that it has positive inotropic activity. Furthermore, the flavonoid components of hawthorn also affect P-gp function and cause interactions with drugs that are P-gp substrates, such as digoxin. In practice, however, results from a randomised crossover trial that evaluated co-administration of digoxin 0.25 mg with *Crataegus* special extract WS 1442 (hawthorn leaves with flowers) 450 mg twice daily for 21 days found no significant difference to any measured pharmacokinetic parameters (Tankanow et al 2003). Although this is reassuring, combined use should be supervised by a healthcare professional and drug requirements monitored.

In practice, the likelihood and significance of these interactions varies considerably, and the response required to ensure safe use of medicines can be multifaceted. For example, if Mr A has been taking St John's wort for several months and then digoxin is introduced, routine monitoring of digoxin levels enables appropriate doses to be determined and ensures the safe use of both medicines. However, it is essential to advise Mr A to inform his healthcare professional when use of St John's wort is going to be ceased or the dosage changed, as digoxin levels will require closer monitoring during the change. On the other hand, if Mrs B has been taking digoxin for some time and then St John's wort is to be introduced, additional monitoring is required for at least 3 weeks to determine whether a new effective digoxin dose is required. Once again, if there is to be an alteration to St John's wort use, Mrs B should be advised to see a healthcare professional for monitoring during the transition.

Interference with therapeutic drug monitoring for digoxin

In 1996, a case was reported of a possible interaction between Siberian ginseng and digoxin (McRae 1996). More specifically, it involved an elderly man whose serum digoxin levels rose (but did not produce toxic symptoms) when he concurrently took a Siberian ginseng product, fell when the product was stopped, and then rose again when use was resumed. Unfortunately, the report was inaccurate, as the product was later analysed and found to contain digitalis. Additionally, no case reports suggesting drug toxicity were published over the following years. Research published earlier this year suggests that eleutherosides found in the herb are chemically related to cardiac glycosides and may interfere with digoxin assays. Furthermore, several other herbal medicines have been identified with the ability to interfere with drug monitoring for digoxin, such as Dan Shen, Chan Su, *Uzara* root and Asian ginseng (Dasgupta 2003). According to Dasgupta, monitoring free digoxin eliminates the interference from Dan Shen and Chan Su, but is not useful in overcoming interference by Siberian or Asian ginseng. For these herbs, using the EMIT urine test or the Bayer, Randox, Roche or Beckman assays is appropriate.

WARFARIN

Warfarin is an important anticoagulant drug with a narrow therapeutic index. If blood levels become elevated, potentially serious

TABLE 8.7 Suspected or known interactions between Digoxin and Herbal Medicines

Increased digoxin effects possible	Decreased digoxin effects possible
Herbs that induce potassium loss with long-term use: • *Glycyrrhiza glabra* (licorice) • *Paullinia cupana* (guarana) • Anthraquinone-containing herbal laxatives (senna, cascara, aloes and buckthorn) Some herbal diuretics may also induce some degree of potassium loss; however, clinical significance is unknown.	Herbs currently known to induce P-gp and/or CYPs in a clinically significant manner: • *Hypericum perforatum* (St John's wort)
Herbs containing cardiac glycosides: • *Nerium oleander* (oleander) • *Adonis autumnalis* (false hellebore) • *Convallaria majalis* (lily of the valley)	Herbs containing > 50,000 ppm potassium: • *Avena sativa* (oats) • *Taraxacum officinale* (dandelion) • *Apium graveolens* (celery)
Pharmacodynamic interaction theoretically possible, although not seen in one clinical study: • *Craetagus oxyacantha* (hawthorn)	Foods containing >50,000 ppm potassium: • asparagus • beetroot • bok choy • cucumber • lettuce • rhubarb • spinach
Herbs and natural constituents known or suspected to inhibit P-gp or CYPs: • apple juice • curcumin • daidzein • genistein • grapefruit • green tea polyphenols • orange juice (seville oranges) • piperine • quercetin • resveratrol • rosemary extract	

consequences can arise if bleeding complications develop, whereas reduced blood levels can result in failure to protect the patient from thromboembolic events. Pharmacologically, the anticoagulant effect is dependent on its ability to interfere with hepatic synthesis of vitamin K-dependent clotting factors. As such, any significant changes to vitamin K ingestion can alter the drug's activity. Common foods with high vitamin K levels (> 100 micrograms/100 g) are: beef (liver), broccoli, cabbage, cauliflower, egg yolk, kale, lettuce, spinach, canola oil (rapeseed) and soybean oil.

Pharmacodynamic interactions

Pharmacodynamic interactions can theoretically occur when other medicines with coagulant or anticoagulant activity are used concurrently. Medicines with antiplatelet activity, such as ginger and garlic, can theoretically increase the risk of bruising or bleeding when taken concurrently with warfarin. Other herbal medicines suspected to potentiate the pharmacological effects of warfarin include guarana and bilberry in very high doses. Alternatively, herbs containing naturally occurring coumarins exhibit weak anticoagulant activity, if any at all (unless converted to dicoumarol as a result of improper storage), so do not necessarily pose an additional bleeding risk (see also Chapter 9).

The case of *Ginkgo biloba* is a curious one, as there is evidence that one of its components, ginkgolide B, is a potent platelet-activating factor antagonist (Smith et al 1996). However, three placebo-controlled studies have failed to detect a significant effect on platelet function or coagulation (Bal Dit et al 2003, Jiang et al 2005, Kohler 2004). One was an escalating dose study, which found that 120 mg, 240 mg or 480 mg given daily for 14 days did not alter platelet function or coagulation (Bal Dit

et al 2003). Interaction studies have further found that the INR does not increase when patients are concurrently taking *Ginkgo biloba* with warfarin (Engelsen et al 2002, Jiang et al 2005). Owing to the serious nature of such potential interactions, a cautious approach is advised.

Pharmacokinetic interactions

Warfarin consists of a pair of enantiomers and is extensively metabolised by CYP1A2, 3A4 and 2C9. Metabolism of the more biologically active isomer, the S form, occurs chiefly by CYP2C9, whereas a minor metabolic pathway is CYP3A4. The less potent R isomer is chiefly metabolised by CYP1A2. Therefore, any alteration to the expression or activity of these specific enzymes can affect the drug's pharmacokinetics.

As is the case with nearly all herbal medicines, predicting the clinical significance of these theoretical interactions is difficult because most evidence currently comes from in vitro and in vivo tests and case reports.

THE RATIONAL USE OF HERBAL AND NATURAL MEDICINES

Overall, when manufactured and prescribed appropriately, the safety of herbal and natural medicines is high. Serious adverse effects and dangerous interactions are rare, particularly in comparison with the thousands of reports attributed to pharmaceutical medicines. Even so, the assessment of adverse reaction and interaction likelihood should remain integral to patient management.

Currently, there are few large-scale clinical studies confirming and clarifying the clinical significance of most suspected interactions, so the two algorithms presented in this chapter should be used only as general guides. As always, it is important to recognise that using this information in practice requires individual interpretation, because the clinical effects of any interaction, no matter how well documented, will not occur consistently in each patient, each time or to the same degree of intensity. Ultimately, it is the application of current knowledge together with good observational skills, open communication and clinical experience that will reduce the risk of unwanted interactions and maximise successful outcomes. Table 8.8 lists key steps towards the rational use of herbal and natural medicines.

TABLE 8.8 Rational Use of Herbal and Natural Medicines

- Be informed and seek out unbiased information — do not rely on label claims alone.
- Know the benefits, risks, potential adverse reactions and interactions — additional training and/or access to accurate and updated information is important.
- Do not assume all healthcare professionals have the knowledge to monitor safe use.
- Be aware that medical practitioners' and pharmacists' knowledge of herbal and natural medicines may be limited.
- Ensure that all healthcare professionals involved in a patient's care stay informed of herbal and natural medicine use.
- Take care with children, the elderly, and pregnant or lactating women.
- Take care when high-risk medicines are being taken.
- Take care with HIV, cancer or other serious illnesses.
- Know the manufacturer or supplier details.
- Store medicines appropriately.

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CHAPTER 9
PREOPERATIVE CARE: CONSIDERATIONS

Reducing the risk of surgery and maximising successful outcomes is the common effort of surgeons, anaesthetists, physicians, nurses and other healthcare professionals. However, few consider the influence of herbal and natural medicines and whether this has the potential to alter outcomes. Even fewer consider the effects of these medicines after surgery. This chapter explores the potential of herbal and natural medicines to hinder surgical outcomes and also introduces the concept of using these medicines beneficially.

EXTENT OF CM USE

According to a number of hospital surveys conducted in the United States and in Australia, use of complementary medicines (CMs) is well established among surgical patients (Braun et al 2006a, Grauer 2004, Kaye et al 2000, Leung et al 2001, Norred 2002, Norred et al 2000, Silverstein & Spiegel 2001, Tsen et al 2000).

One survey of 3106 patients attending preoperative clinics in the USA found that 51% were using CMs, and that women were more likely users than men (Tsen et al 2000). Age was also a factor, with patients aged between 40 and 60 years greater consumers of CMs. Overall, only 21% of patients sought advice from a healthcare provider about supplement use, whereas the majority cited friends and family or their own decision as reasons for taking these medicines.

Another survey of 1017 patients presenting for pre-anaesthetic evaluation found that approximately one in three were taking one or more herb-related compounds (Kaye et al 2000). Disturbingly, nearly 70% of these patients did not report use when they were asked during routine anaesthetic assessment. Lack of communication was also detected in a review of 2560 patients, which identified that 39% were taking natural supplements, with herbal medicines being the most popular (Leung et al 2001). Of these, 44% did not consult with their primary-care physician and 56% did not inform their anaesthetist before surgery.

Similar trends have also been identified among Australian surgical patients (Braun et al 2006a, Grauer 2004). A survey of 508 presurgical inpatients at two tertiary hospitals found that in the 2 weeks before admission, 46% had used CMs, of which 38% were self-prescribed (Braun et al 2006a). Just over half these patients planned to continue using them while in hospital. During the 2 weeks before admission, 64% had not discussed use with any community-based or hospital-based healthcare professional. Similar to findings of other studies, patients using CMs were most likely to be female, and to have pursued higher education and earn above-average income. Interestingly, this study found that age was not predictive of use, and that older patients were just as likely as young patients to be using CM. Importantly, 58% of surgical patients did not discuss their use with a hospital doctor, nurse or pharmacist. When patients were asked why they did not tell hospital staff, it was not because they feared being judged negatively, but overwhelmingly because they were not asked. This was also the first Australian study to ask patients about their interest in hospital-based CM therapies; 85% expressed an interest.

Previously, a study that evaluated preoperative use of CM products at two other hospitals had found that 20.4% had used vitamin

supplements and 14.3% herbal medicines in the previous 6 weeks, but only 28% had informed hospital staff about use (Grauer 2004). Once again, the majority of patients had self-selected their treatment.

These findings pose several important questions, such as whether surgeons, anaesthetists, physicians or pharmacists are aware of the potential safety issues associated with CMs, routinely ask patients about herbal and natural medicines in a way that encourages open dialogue, and have the knowledge and resources to interpret the answers. Survey results published in 2001 found that, although physicians did ask about herbal and natural medicine use, most did not check with reference texts for more information (Silverstein & Spiegel 2001). Disturbingly, the survey also detected an obvious lack of knowledge about common herbal medicines among physicians. A more extensive study was conducted recently with hospital doctors and pharmacists at an Australian tertiary hospital (Braun et al 2006b). The study of 127 surgeons, anaesthetists, physicians and pharmacists found that 68% thought CMs could be dangerous and that patients' use needs to be monitored; however, only 28% routinely asked patients about CM use. All groups lacked knowledge and confidence in dealing with CAM, and 81% felt they had insufficient knowledge to be able to identify whether a CM product could adversely affect patient care. Despite this, few checked for side effects or interactions when patients using CMs were identified.

When patients do report using herbal and natural medicines, hospital doctors and pharmacists do not routinely document this information in patients' charts, making effective communication even more difficult (Braun et al 2006b, Cohen et al 2002). Cohen et al (2002) found the prevalence of supplement use was 64% in a group of 212 patients, but only 35% of all supplements were recorded in patients' charts.

ASSESSING POTENTIAL FOR ADVERSE EFFECTS

The use of CAM by surgical patients should not pose any serious concern, unless they have the potential to cause adverse reactions that would negatively affect the outcome of surgery and impede recovery. Potential unwanted effects such as increased bleeding risk, sympathomimetic effects or detrimental interactions with medicines commonly used in the perioperative period are some examples.

Two studies conducted in the United States have investigated this further and suggest that some CM products used by surgical patients have the potential to alter bleeding risk, cardiovascular stability and interact with anaesthetics. A survey of 500 elective surgical patients found that 51% used CAM products during the 2 weeks before surgery, and that 27% of CMs taken had the potential to inhibit coagulation, 12% to affect blood pressure, 9% to cause sedation, 5% to have cardiac effects and 4% to alter electrolytes (Norred et al 2000). A larger survey of elective outpatients from 16 hospitals in the United States found that 67% used herbal and natural supplements or homoeopathic medicines and, of these, 34% used medicines that had the potential to interact with anaesthetics or to inhibit coagulation (Norred 2002). A review of the medicines used identified garlic (9.5%), cranberry (5.2%), ginkgo (4.6%), ginseng (4.2%), echinacea (4.1%) and products containing ephedra (3.2%) as the most commonly consumed herbal medicines, whereas multivitamins (37.5%), vitamin E (23.3%), calcium (21.5%) and vitamin C (21.4%) were the most commonly taken nutritional supplements.

Although useful, the results obtained by these two papers should be interpreted carefully because much of the safety information presented is speculative and based on studies conducted in other populations or test models. Close inspection of the lists of herbal and natural supplements claimed to inhibit coagulation reveals that no distinction is made between those medicines with clinically observed effects and those with predicted effects based on in vitro or in vivo evidence. Furthermore, the majority of claims made about adverse reaction potential are based on case reports and in vitro and in vivo tests, and not on controlled clinical trials. Without documenting where evidence comes from for each claim, readers can easily give equal weight to all claims, making the lists of limited clinical value and likely to overstate the risk. Additionally, both papers fail to state full botanical names when referring to herbal medicines and are open to misinterpretation.

Developing a list of herbal and natural supplements with a realistic potential to cause adverse effects in surgery is difficult at the current time, as the pharmacology of many of these medicines, including pharmacodynamic and pharmacokinetic properties, has yet to be fully elucidated. Until evidence from controlled

clinical studies is available, other evidence will be used but should be interpreted cautiously.

SAFETY, SIDE EFFECTS AND INTERACTIONS WITH OTHER MEDICINES

The risk of harm associated with the use of CMs is largely unknown; however, it is likely to be greatest in high-risk surgery; that is, when the surgical procedure to be undertaken and the patient's health status put the patient at real risk of serious complications. Factors such as preexisting fluid and electrolyte status, cardiorespiratory performance, comorbidities and medical pretreatments need to be considered when assessing safety in patients (Girbes 2000). Additionally, the type of surgical procedure should be considered, in particular those procedures in which increased bleeding would be a serious complication (e.g. orthopaedics or neurosurgery) or put significant physical strain on the patient (e.g. coronary bypass) would be considered high risk.

BLEEDING RISK

Surgery is often associated with some degree of blood loss, but this is usually limited by the body's haemostatic mechanisms, which finely regulate interactions between components on the blood vessel walls, circulating platelets and plasma proteins. A retrospective survey of adverse surgical outcomes in several US hospitals found that postoperative bleeding accounted for 10.8% of all surgical adverse events, making it the third most frequent adverse surgical event (Gawande et al 1999). In practice, whether bleeding risk is a serious concern is usually dictated by the type of surgery to be undertaken. For instance, minor dental procedures would not be as seriously affected by increased bleeding as neurosurgery.

A number of explanations may account for increased bleeding, such as undiagnosed clotting disorders, liver disease or the preoperative use of certain medicines such as antiplatelet agents. Over time, it has become recognised that some CMs also have the potential to influence the body's haemostatic response. Initially evidence was derived from case reports suggesting CM use was associated with bleeding or from in vitro tests indicating antiplatelet activity; however an increasing number of clinical studies are now being published to more rigorously determine which CAM products cause clinically significant bleeding.

Herbal medicines and food supplements

Whether preoperative use of herbal medicine alters bleeding risk is difficult to determine because few controlled trials are available for this specific population. Evidence is usually extrapolated from other sources to identify those medicines with suspected antiplatelet or anticoagulant activity and, while still largely speculative, this provides a guide until more robust evidence is available.

Difficulties arise when evidence is contradictory, making clinical recommendations even more difficult. The herb *Tanacetum parthenium*, also known as feverfew, provides a good example. Several test-tube studies and animal models have observed inhibition of platelet aggregation (Heptinstall et al 1988, Jain & Kulkarni 1999, Makheja & Bailey 1982); however, no significant effects were seen in a small study of 10 patients receiving feverfew (Biggs et al 1982). The problem of inconsistent information can add to practitioners' confusion, as some databases are infrequently updated or give undue weight to case reports and seemingly less consideration of safety information derived from clinical studies. The case of ginkgo biloba illustrates this point.

Ginkgo biloba

Ginkgo biloba is a popular herbal medicine used mainly for cognitive decline and peripheral vascular diseases, supported by good evidence. Concern over whether *G. biloba* significantly increases bleeding first arose in response to several case reports describing haemorrhage during or after surgery (Hauser et al 2002, Schneider et al 2002) and evidence that one of its components, ginkgolide B, is a platelet-activating factor antagonist (Smith et al 1996). In the following years, at least 10 clinical studies have been conducted that have found no evidence of significant bleeding or platelet effects due to *G. biloba* ingestion (Bal Dit et al 2003, Engelsen et al 2003, Kohler et al 2004, Jiang et al 2005, Wolf 2006, Beckert et al 2007, Gardner et al 2007, Aruna & Naidu 2007, Lovera et al 2007, Carlson et al 2007). Studies have included young healthy volunteers, older adults, people with multiple sclerosis and people using warfarin or aspirin at the same time as *G. biloba*. An escalating-dose study found that 120 mg, 240 mg or 480 mg given daily for 14 days did not alter platelet function or coagulation (Bal Dit et al 2003). Only one clinical study demonstrated that EGb761 (80 mg/day) produced a significant

reduction in blood viscosity after 30 days' treatment (Galduroz et al 2007). When the available body of evidence is considered, it appears unlikely that *G. biloba* causes a significant bleeding risk to most patients. Unfortunately, a number of popular electronic databases and reference texts still cite bleeding risk as a major concern with its use, particularly when used in combination with warfarin (Braun 2008).

Food supplements contain concentrated forms of dietary foods, such as fish oils or fibre. Herbal and food supplements overlap in many cases because various herbs are also eaten as foods (e.g. ginger). Keeping this in mind, it is not unusual to find evidence suggesting that normal dietary intake of a food does not appreciably alter bleeding risk, whereas ingesting concentrated products will. For example, 4 g ginger daily does not alter platelet aggregation or fibrinogen levels according to one clinical study, whereas a dose of 10 g/day significantly reduces platelet aggregation according to another (Bordia et al 1997).

Commonly used herbal medicines and food supplements available OTC that have been found to inhibit platelet aggregation under clinical test conditions include garlic, ginger root, onion, policosanol and pine bark extract (Araghi-Niknam et al 2000, Arruzazabala et al 2002, Bordia et al 1975, 1997, Harris et al 1990, Jung et al 1991). Often, very high doses above normal dietary intakes are required to produce these results.

Fish oils

Fish oils supplements are extremely popular and are considered by some healthcare professionals to increase the risk of bleeding in surgery. A search through the Medline database reveals several case reports where bleeding episodes are attributed to fish oil ingestion (Buckley et al 2004, Jalili & Dehpour 2007, McClaskey & Michalets 2007). In each case, the person affected was elderly and also taking warfarin. One was a report of an elderly man taking high-dose omega-3 fatty acids (6 g/day) with both aspirin and warfarin who developing a subdural haematoma after a minor fall (McClaskey & Michalets 2007). Another case is reported of a 67-year-old woman taking warfarin for 1.5 years who doubled her fish oil dose from 1000 to 2000 mg/day, causing an associated elevation in INR from 2.8 to 4.3 within 1 month (Buckley et al 2004). A third case was of a 65-year-old male who had been taking warfarin for 6 months and then was recommended trazodone and fish oils, causing his INR to rise to 8.06 (Jalili & Dehpour 2007).

Although these case reports suggest omega-3 fatty acids interact with warfarin and increase the risk of bleeding, several intervention studies have come to a different conclusion. One randomised study of 511 patients taking either aspirin (300 mg/day) or warfarin (INR 2.5–4.2) found that a dose of 4 g/day of fish oils did not increase the number of bleeding episodes, bleeding time or any parameters of coagulation and fibrinolysis (Eritsland et al 1995). A smaller placebo-controlled study by Bender et al (1998) of patients receiving chronic warfarin therapy found that fish oil doses of 3–6 g/day produced no statistically significant difference in INR between the placebo lead-in and treatment period within each group. There was also no difference in INR between groups.

Most recently, Harris (2007) examined 19 clinical studies that used doses of fish oil varying from 1 g/day to 21 g/day in patients undergoing major vascular surgery (coronary artery bypass grafting, endarterectomy) or femoral artery puncture for either diagnostic cardiac catheterisation or percutaneous transluminal coronary angioplasty. Of note, in 16 studies patients were taking aspirin and in 3 studies patients were taking heparin. The review concluded that the risk of bleeding was virtually non-existent. Frequent comments accompanying the studies were 'no difference in clinically significant bleeding noted' or 'no patient suffered from bleeding complications'. The same conclusion was reached in a 2008 review that stated no published studies have reported clinically significant bleeding episodes amongst patients treated with antiplatelet drugs and fish oils (3–7 g/day) (Harris et al 2008). In light of this body of evidence, it is apparent that fish oil supplementation does not significantly increase bleeding risk.

Emerging evidence further suggests that administration of fish oil to presurgical patients before cardiothoracic surgery has significant benefits, such as reduced rate of postoperative atrial fibrillation (Calo et al 2005). Such benefits have major implications for patients, hospital administrators and hospital waiting lists.

Salicylate-containing herbs

Many salicylate-containing herbs, such as willowbark and meadowsweet, are suspected of having blood-thinning activity based on their chemical relationship to aspirin. When these

herbs are ingested, salicylic acid is formed, which accounts for some of their anti-inflammatory and antipyretic activity. The synthesis of aspirin involves adding an acetyl group to salicylic acid, which not only reduces the irritant effect of the salicylic acid but also confers an antiplatelet effect. The conversion of salicylic acid to acetylsalicylic acid does not occur in the body, so it is unlikely that these herbs will have an appreciable effect on bleeding (Forrelli 2003). This has been borne out in a clinical study, which found that a therapeutic dose of *Salicis cortex* extract (willowbark containing 240 mg salicin per daily dose) produced a total serum salicylate concentration bioequivalent to 50 mg acetylsalicylate, which had a minimal effect on platelet aggregation (Krivoy et al 2001).

Coumarin-containing herbs

A similar confusion has arisen surrounding the presence of naturally occurring coumarin compounds in herbs. Coumarin compounds are benzo-alpha-pyrones and are found in popular herbal medicines such as dong quai, alfalfa, celery, fenugreek and red clover. Nearly all natural coumarin compounds contain a hydroxyl or methoxy group in position 7, whereas dicoumarol and related anticoagulants are hydroxlated in the 4 position (Bone & Mills 2000). This difference in chemical structure is important because it influences the entity's potential to induce significant anticoagulant activity. It has been estimated that natural coumarins, which naturally are not substituted at the 4 position, have one-thousandth the anticoagulant activity of dicoumarol, so are unlikely to cause significant bleeding episodes (Bone & Mills 2000). As an example, a placebo-controlled study failed to identify significant changes to platelet aggregation, fibrinolytic activity or fibrinogen for the herbal medicine fenugreek, even though it contains naturally occurring coumarins (Bordia et al 1997).

Nutritional supplements

The safety of using preoperative nutritional supplements is also largely based on suspected antiplatelet or anticoagulant activity and is poorly researched. As such, identifying key supplements that increase bleeding risk is not straightforward and contradictory evidence also exists. Vitamin E provides a good example.

Although widely cited as affecting bleeding times, clinical studies with vitamin E supplements have produced conflicting results in recent years. According to one clinical study, a daily dose of 1200 IU of vitamin E (800 mg of D-alpha-tocopherol) taken for 28 days had no effect on platelet aggregation or coagulation compared with controls (Morinobu et al 2002). A dose of 600 mg (900 IU) of RRR-alpha-tocopherol taken for 12 weeks did not alter coagulation activity compared with placebo in another clinical study (Kitagawa & Mino 1989). However, doses of 75 IU and 450 IU have been shown to decrease platelet aggregation in human subjects in other studies (Calzada et al 1997, Mabile et al 1999).

ELECTROLYTE STATUS AND BLOOD-PRESSURE EFFECTS

Whether preoperative use of CAM products significantly alters electrolyte status or blood pressure and thus increases the surgical risk is unknown and still largely speculative. Controlled trials are unavailable, so evidence is extrapolated from other sources to identify those medicines with suspected activity.

Glycyrrhiza glabra

There are a small number of OTC herbal medicines with the potential to induce hypokalaemia, sodium retention or significant cardiovascular effects. The best documented of these is probably *Glycyrrhiza glabra* (licorice), which has significant pharmacological activity and the potential to cause adverse effects when used long-term in high doses. Determining a dose that is safe for all is difficult, as there is a great deal of individual variation in susceptibility to the herb's effects. One dose-response study that tested licorice in a variety of individuals has identified that doses as low as 50 g (75 mg glycyrrhetinic acid) taken daily for 2 weeks are capable of raising blood pressure in sensitive individuals (Sigurjonsdottir et al 2001). A return to baseline levels may take several weeks according to Commission E (Blumenthal et al 2000) and is also likely to vary between individuals.

G. glabra raises blood pressure and produces oedema by significantly decreasing serum concentrations of cortisol, ACTH and aldosterone, and increasing renin and sodium levels in a dose-dependent manner (Al Qarawi et al 2002). Glycyrrhetinic acid is the main constituent responsible, causing an 11-beta-hydroxylase deficiency secondary to an inability to convert 11-deoxycortisol or deoxycorticosterone into active glucocorticoids, cortisol and corticosterone (Heilmann et al 1999).

Paullinia cupana

Based on the herb's caffeine content and diuretic activity, *Paullinia cupana* (guarana) may potentially induce hypokalaemia and unwanted cardiovascular effects when used in excessive doses. Although these effects have not been tested in controlled clinical settings, results obtained for caffeine and the following case report provide some evidence of cardiovascular activity. A 25-year-old woman with preexisting mitral valve prolapse was reported as developing intractable ventricular fibrillation after consuming a 'natural energy' guarana health drink containing a high concentration of caffeine (Cannon et al 2001).

Panax ginseng

Despite *Panax ginseng*'s reputation for altering blood pressure, current evidence is contradictory and difficult to assess. Both hypotensive and hypertensive effects have been observed in animal studies with this herb, which is also known as Korean ginseng. However, interpreting the significance of these results is difficult, because injectable forms are sometimes used. Clinical observations are also contradictory, with both elevations and reductions in blood pressure having been reported (Valli et al 2002).

TISSUE PERFUSION AND REPERFUSION INJURY

Unfortunately, many critically ill surgical patients survive surgery only to die of infection or organ dysfunction over the ensuing days or weeks (Nathens et al 2002). The precise mechanism by which organ dysfunction occurs is unclear; however, there is increasing evidence that tissue injury is mediated at least in part by reactive oxygen species derived from inflammatory cells and the vascular damage caused by ischaemia–reperfusion injury. Based on this theory, research has begun to investigate the effects of pre- and postsurgical treatment with several medicines, such as antioxidant supplements. Probably the most research conducted to date has involved coenzyme Q10.

Coenzyme Q10 pretreatment

Clinical studies investigating the effects of oral coenzyme Q10 (CoQ10) supplementation before cardiac surgery suggest it may improve postoperative cardiac function, efficiency of mitochondrial energy production, reduce intraoperative myocardial structural damage and significantly reduce hospital stays (Chello et al 1996, Chen et al 1994, Judy et al 1993, Rosenfeldt et al 2002, Taggart et al 1996, Tanaka et al 1982, Zhou et al 1999).

One placebo-controlled study involving 100 patients investigated the effects of oral CoQ10 (30–60 mg) taken 6 days before surgery and found that treatment significantly lowered the incidence of low cardiac output during recovery (Tanaka et al 1982). These results suggest that presurgical treatment with CoQ10 increased myocardial tolerance to ischaemia during surgery. A smaller, randomised double-blind study also found reduced incidence of low cardiac output during recovery with CoQ10 pretreatment and a lowered incidence of elevated left atrial pressure (Chen et al 1994). Additionally, ventricular myocardial structure was better preserved in patients receiving CoQ10 before surgery, as measured by electron microscopy.

Besides having beneficial effects on cardiac output, pretreatment with CoQ10 has a number of other effects. A randomised, placebo-controlled study of 40 patients undergoing elective coronary artery bypass found that CoQ10 (150 mg/day) taken for 7 days before surgery produced a significantly lower incidence of ventricular arrhythmias during the recovery period compared with placebo (Chello et al 1994). Additionally, mean dopamine dosage required to maintain stable haemodynamics was significantly lower with CoQ10 pretreatment. One placebo-controlled study involving high-risk surgical patients used 100 mg/day CoQ10 for 14 days before surgery and for 30 days afterward (Judy et al 1993). This treatment regimen dramatically hastened the recovery to 3–5 days, compared with 15–30 with a placebo, and significantly reduced the incidence of complications.

A recent randomised, double-blind trial investigated the effects of preoperative high-dose CoQ10 therapy (300 mg/day) in patients undergoing elective cardiac surgery (mainly coronary artery bypass graft surgery or valve replacement) (Rosenfeldt et al 2005). The study of 121 patients found that approximately 2 weeks of active treatment resulted in significantly increased CoQ10 levels in the serum, atrial myocardium and mitochondria compared to a placebo; however, no effects on duration of hospital stay were seen. Active treatment improved subjective assessment of physical QOL (+13%) in the CoQ10 group compared with the placebo; however, the authors point out that physical quality of life

does not necessarily indicate improved cardiac pump function and further studies are required with larger sample sizes to clarify the role of CoQ10 in cardiac surgery.

Most recently, a 3-year prospective randomised clinical trial was completed at the Alfred Hospital in Melbourne. This involved 117 patients of mean age 65 years who were undergoing elective coronary artery bypass graft and/or valve surgery with or without coronary bypass (Leong et al 2007). Coenzyme Q10 (300 mg/day) was administered together with other natural metabolic agents (magnesium orotate 1200 mg/day, alpha lipoic acid 100 mg/day, omega-3 fatty acids 3000 mg/day and selenium 200 μg/day) or identical placebos for a minimum of 2 weeks before and 1 month after surgery. Active treatment produced a highly significant reduction in the release of plasma troponin I at 24 hours ($P = 0.003$) postoperatively, indicating reduced cardiac muscle damage. Additionally, patients undergoing coronary artery bypass surgery experienced a significant 50% reduction in postoperative atrial fibrillation. It was also found that patients in the placebo group stayed 17% (6%–30%) longer in hospital than those in the metabolic group ($P = 0.002$). This result equates to an extra 1.3 days. These findings have major implications for patients' long-term mortality, quality of life and hospital costs.

The encouraging results obtained from CoQ10 in cardiac surgery may have special significance for the elderly, because recovery of cardiac function in this group is inferior to younger patients. It has been suggested that the aged myocardium is more sensitive to stress, and may therefore not be as well equipped to deal with the physical stress sustained during surgery. Rosenfeldt et al (1999) confirmed this theory, demonstrating an age-related deficit in myocardial performance after aerobic and ischaemic stress and the capacity of CoQ10 treatment to correct age-specific diminished recovery of function.

Although most clinical research has been conducted in patients undergoing cardiac surgery, one study suggests that pretreatment may have benefits in other situations. The effects of randomly assigned supplemental oral CoQ10 (150 mg/day) in 30 patients undergoing elective vascular surgery for abdominal aortic aneurysm or obstructive aorto-iliac disease abdominal clamping also produced positive results (Chello et al 1996). Pretreatment for 7 days before surgery reduced the degree of peroxidative damage during abdominal aortic cross-clamping compared with that seen in the placebo group.

Although CoQ10 is the most studied antioxidant vitamin supplement for cardiac surgery support, investigation into others has begun.

INTERACTIONS WITH MEDICINES COMMONLY USED DURING SURGERY

An interaction is said to have occurred if there is an alteration to the predicted effect of one substance when it has been given together with

Clinical note — Alfred Hospital's Integrative Cardiac Wellness Program

In recent years the increasing incidence of high-risk and elderly patients presenting for major surgery has presented a challenge for surgeons, due to the associated increased mortality and complication rate and costs. Over the last few years at the Alfred Hospital and the Baker Heart Research Institute, Melbourne, Australia, researchers in the Cardiothoracic Surgical Research Unit, led by Professor Frank Rosenfeldt, have developed regimens of metabolic therapy with the pyrimidine precursor orotic acid, and the antioxidant and mitochondrial respiratory chain component coenzyme Q10. These regimens improve the response of the ageing and failing heart to hypoxia, ischaemia/reperfusion injury and aerobic stress such as occur during cardiac surgery. Omega-3 fatty acids and the antioxidant alpha-lipoic acid have been added to the metabolic cocktail, in light of emerging research showing benefits for this population. The metabolic regimen is now being combined with holistic therapy comprising inpatient and outpatient wellness education to create a novel integrative program of 'perioperative rehabilitation'. This approach is known as the Integrative Cardiac Wellness Program and officially commenced at the Alfred Hospital in 2008.

For more information, see www.thealfred.org.au/icwg/.

another. Owing to this lack of predictability, the term 'interaction' is often given a negative connotation, but interactions can also be manipulated to advantage and offer potential benefits to patients.

As discussed in Chapter 8, herb–drug interactions have not been extensively researched in clinical studies. As such, recommendations are based on the best available evidence at the time of writing, chiefly sourced from primary biomedical literature. Furthermore, clinicians using this information in practice are advised that it requires individual interpretation, as the clinical effects of any interaction, no matter how well documented, will not occur consistently in each patient, each time or to the same degree of intensity.

Although there are myriad different surgical procedures currently being performed in hospitals and day-surgery centres, the same general drug classes tend to be used. These are analgesics and anaesthetics. In both cases, concurrent use of herbal and natural medicines theoretically has the potential to produce unwanted interactions or, alternatively, beneficial interactions.

ANALGESICS

Pain is a complex phenomenon involving both an alteration to normal neuronal activity and an individual's perception of that alteration. As such, the sensation of pain is largely subjective and greatly influenced by psychological factors. A number of different medicines are used to relieve pain in the hospital setting.

Opioid analgesics, such as pethidine and morphine, are effective for most kinds of pain, inducing a sense of calm. Unfortunately, their use is associated with a number of unwanted effects such as nausea and vomiting, reduced gastrointestinal motility, constipation, drowsiness and the development of physical and psychological dependence.

Currently, controlled clinical trials to identify significant interactions are lacking; however, it is possible to make some theoretical predictions. Concurrent use of another medicine that can further induce constipation, nausea or sedation has the potential to make these symptoms more troublesome (e.g. supplements containing calcium, iron, phytostanols or sterols). Medicines that have mild laxative effects, such as dandelion root and herb, psyllium husks, probiotics and yellow dock root, may be beneficial. Besides using CAM products to reduce adverse effects, techniques that can reduce the perception of pain have the potential to augment analgesic effectiveness (e.g. acupuncture, massage, biofeedback, meditation and possibly aromatherapy).

ANAESTHETICS

Local anaesthesia is often used to eliminate pain during minor surgery. Local anaesthetics tend to have an intense and short-lived effect, although this depends largely on the technique of administration and whether a vasoconstrictor agent has been co-administered. General anaesthesia can involve the use of several medicines, in addition to the anaesthetic agent, in order to dry secretions (e.g. antimuscarinic agents), reduce anxiety (e.g. benzodiazepines), produce amnesia and provide postoperative pain relief.

Whether CAM products significantly interact with anaesthetics is largely unknown and still speculative because controlled clinical studies are lacking. Evidence extrapolated from other sources can identify those medicines with pharmacological actions that suggest an interaction is theoretically possible, but clinical significance remains uncertain. For instance, medicines with sedative activity can theoretically prolong or potentiate the sedation induced by the anaesthetic drug combination.

Valeriana officinalis

Both in vivo and numerous clinical studies confirm sedative or hypnotic activity for the herb valerian (see Valerian monograph). Furthermore, valerian has been compared with benzodiazepine drugs in at least three human trials and has been found to be an effective treatment for insomnia (Dorn 2000, Gerhard et al 1996). One double-blind randomised trial involving 202 patients found that valerian extract 600 mg/day (Sedonium) was as effective as 10 mg oxazepam in improving sleep quality over 6 weeks (Ziegler et al 2002). Two clinical studies have found that valerian use is not associated with next morning somnolence, suggesting that the herb is short-acting (Gerhard et al 1996, Kuhlmann et al 1999). While a pharmacodynamic interaction is possible, leading to increased sedation, its short duration of action makes a clinically significant interaction between valerian and general anaesthetics unlikely.

Kava kava

Kava kava produces a significant reduction in anxiety compared with a placebo according to a 2003 Cochrane review, which analysed

results from 12 clinical studies involving 700 subjects (Pittler & Ernst 2003). Preliminary evidence suggests it may be equivalent to benzodiazepines in non-psychotic anxiety. It is also used in insomnia, with some clinical evidence supporting its use. With regard to surgery, kava kava may produce beneficial effects for the anxious patient; however, it could theoretically increase CNS sedation when used with benzodiazepines. Additionally, clinical testing has found that kava kava significantly inhibits (≈ 40%) CYP2E1, which may have implications when used together with CYP2E1 substrates such as halothane, isoflurane and methoxyflurane, causing a rise in drug serum levels (Gurley et al 2005). Kava kava should be used under professional supervision to avoid adverse outcomes.

St John's wort

Based on theoretical considerations, response to agents such as midazolam, diazepam and fentanyl may be reduced with *Hypericum perforatum* (St John's wort) because of pharmacokinetic interactions, whereas a pharmacodynamic interaction may occur with tramadol (Alfaro & Piscitelli 2001). These interactions are based on evidence that St John's wort (products containing the hyperforin constituent) induces cytochrome 3A4 and P-glycoprotein, as well as upregulating both 5-HT_{1A} and 5-HT_{2A} receptors and exerting a SSRI-like effect (see St John's wort monograph for more detail).

RECOMMENDATIONS BEFORE HIGH-RISK SURGERY

Appendix 5 is included in this book to provide clinicians with guidance when advising patients due for surgery about the safe use of CMs. It is limited to the 130 CMs reviewed in this book and focuses on those that are known or suspected to increase bleeding or interact with drugs commonly used in the perioperative period. The recommendations are conservative and not likely to be relevant to many low-risk patients or those undergoing minor surgical procedures; however, it is imperative that each patient be individually assessed before surgery.

CMs are listed alphabetically by common name. The comments section includes a brief description of the type of evidence available to support the recommendation; more detailed information is given in individual monographs. Several different recommendations are possible. Sometimes there is a recommendation to suspend use 1–2 weeks before surgery, which should provide ample time for bleeding rates to return to normal or potential interactions to be avoided. This is most likely an overestimation of the actual time required. Please note that coumarin-containing and salicylate-containing herbs have not been included in Appendix 5 unless they have demonstrated antiplatelet or anticoagulant effects in animal or human studies. In some cases, the recommendations are dose-dependent; in others, CM use appears safe but there is a theoretical concern.

It is acknowledged that, in practice, not all surgical patients will be able to follow these recommendations. In situations where bleeding would be a serious complication and a 1-week minimum deferment is not possible, tests of haemostasis before surgery should be considered.

It must be reiterated that the clinical relevance of some interactions and adverse effects is unknown and controlled studies in surgical patients are not available. However, it would seem prudent for healthcare providers to become familiar with these medicines, in order to advise patients appropriately and anticipate, manage or avoid adverse events during the perioperative period.

PATIENT-CENTRED ASSESSMENT AND MANAGEMENT DURING PERIOPERATIVE CARE

The term 'evidence-based patient choice' (EBPC) is the merging together of two important modern movements in Western healthcare, namely evidence-based medicine and patient-centred care. Evidence-based medicine requires the use of the best available evidence to make decisions about medical management. However, the individual qualities, needs and preferences of patients have sometimes been neglected as relevant factors in the decision-making process. Models of EBPC advocate shared decision making, in which patients have received the appropriate evidence for their situation and are able to communicate their personal preferences (Ford et al 2003).

QUALITY USE OF MEDICINES

Inspired by the World Health Organization, countries around the world are developing and instigating policies to ensure medicines are of acceptable safety, quality and efficacy and are accessible. At the end of 1999, Australia launched its National Medicines Policy. In

order to achieve one of the key goals of this policy, the National Strategy for the Quality Use of Medicines was developed (for more information see www.health.gov.au).

The goal of the Quality Use of Medicines (QUM) strategy is to optimise the use of medicines to improve health outcomes. It attempts to adopt EBPC into its framework, recognising that QUM requires the collaborative effort of a 'medication team' made up of doctors, pharmacists, nurses and patients. It advises also that CAM products be included in assessing a patient's medication situation. In practice, this step appears to be problematic and handled very differently by hospitals.

AUSTRALIAN HOSPITALS: POLICIES AND PROBLEMS

Although the task of getting the right medicine to the right patient should be straightforward, it is rarely the case, according to an editorial in the *Journal of Pharmacy Practice and Research* (Ryan 2003). It has been suggested that many participants are involved in the process; some of these are obvious, such as surgeons, physicians and pharmacists, and some less obvious, such as the manufacturer, pharmacy wholesaler, hospital nurse and medical educators. In the case of CMs, it is very complicated. Although hospitals should ideally respect the autonomy of patients who make informed decisions about the interventions they feel are in their best interests, they also have a duty of care. They are generally reluctant to administer herbal medicines or other substances that are not part of the standard hospital formulary, are of unknown quality and may have potential adverse effects with variable evidence of efficacy or require specific knowledge in their preparation or administration.

As a result, a number of hospitals have developed local policies that range from disallowing use of CMs (which includes herbal and natural medicines by definition) to treating these medicines as the 'patient's own'. Both approaches are problematic. Advising patients to discontinue taking all herbal and natural medicines before surgery may not free patients from risk relating to their use because withdrawal may be detrimental, in much the same way that withdrawal of some pharmaceutical medicines is associated with increased morbidity after surgery. Treating these medicines as 'the patient's own' may also provide false security, because their use may not be adequately monitored or considered in treatment and discharge plans.

The development of hospital policy and guidelines that take into account the principles of EBPC and QUM in regard to the use of CMs is no doubt very challenging, and finding consensus among all members of the 'medication team', administration bodies and patients is a difficult task. The New South Wales Therapeutic Assessment Group has developed a useful discussion paper about the use of CAM in public hospitals (see http://www.ciap.health.nsw.gov.au/nswtag/publications/otherdocs/complementary_medicines_public_hospitals_200010.pdf).

RECOMMENDATIONS

At various stages of the preoperative course, different healthcare professionals can intervene to ensure the patient is optimally prepared for surgery.

If anaesthesia is to be performed, a preoperative consultation is conducted by the attending anaesthetist. According to the Australian and New Zealand College of Anaesthetists (ANZCA), the consultation consists of a concise medical history, physical examination, a review of results of relevant investigations and current medications (see http://www.anzca.edu.au). Although not officially stated, this includes CMs. Currently in the United States, the American Society of Anesthesiologists recommends the discontinuation of all herbal medicines 2 weeks before elective surgery. In Australia and New Zealand, the situation is different because the ANZCA does not make the same general recommendation, instead relying on each anaesthetist to make an individual assessment.

Increasingly, hospital pharmacists are taking on the role of conducting presurgical medication reviews to improve patient safety. Although the focus is on the use of pharmaceutical medicines, the use of CMs is increasingly recognised and included in the medication discussion. Eight practice tips to promote patient safety and welfare are provided as a guide for all health care providers managing patients taking herbs and natural supplements during the preoperative period.

UNMANAGED INTEGRATED HEALTHCARE

Currently it appears that a number of patients are already receiving what could be described as unmanaged integrated healthcare, because they are taking herbal and natural medicines and sometimes consulting with a non-medical

EIGHT PRACTICE TIPS TO PROMOTE PATIENTS' WELFARE AND SAFETY

1. Ask all patients about the use of CMs.
According to the literature, many patients fail to disclose use of CMs to hospital staff; however, disclosure is more likely to occur if they are asked directly. Some patients may not understand what is meant by the term 'complementary medicine' so consider using phrases such as 'vitamins, minerals or herbal medicines' or 'natural medicines'. It will also be useful to determine whether the product was professionally prescribed or self-selected.

2. Suspend use of complementary medicines known or suspected to pose a safety risk 5–7 days before surgery, where appropriate.
According to the literature, a washout period of 5–7 days should be sufficient to ensure most CMs no longer present a safety concern (Ang-Lee et al 2001). If this is not possible or advisable, be aware of the potential problems and manage accordingly.

3. If in doubt, refer to drug information centres, peer-reviewed literature or reputable resources for further information.
Evidence is accumulating about CAM at a rapid rate, and it would be unreasonable to expect all healthcare professionals to keep up to date with these changes. However, referring to reputable information sources when unsure about patient safety is essential for best practice. This may involve referring to CAM practitioners with the appropriate training and expertise.

4. Document information and recommendations in patient's chart.
Patient's CM use should be documented in the medication history and/or discharge summary as appropriate. The name, strength, brand and dose used should be recorded.

5. To continue use of CMs or not?
If a patient is experiencing benefits from the use of a CM, and the available evidence indicates efficacy and safety, use should be continued, but monitored. If a patient is using a CM with known or suspected potential to cause adverse outcomes, an honest discussion about what is known and not known about the risks should ensue. If the patient still wishes to continue using the CM against professional advice, they should be asked to sign an acknowledgment form that informs them of the potential adverse effects and that their attending doctor or pharmacist has recommended against continued use. This should also be documented in the patient's medication history and/or discharge summary.

6. Consider if and when a patient can resume taking the CM.
If use of an effective CM has been withdrawn, recommencement will be required to restore the patient's response. This should be discussed when taking the medication history.

7. Recommend CMs with known safety and benefit.
If research indicates a CM has significant benefits during the perioperative period, then evidence-based practice dictates it should be considered in the patient's management.

8. If an adverse event does occur, report this through the relevant channels.
Little research is available to determine the clinical significance of CMs in the perioperative period. As such, case reports provide useful clues that can guide future research to better determine factors affecting patients' safety.

practitioner while being prescribed pharmaceutical medicines and consulting medical practitioners.

The ultimate aim of surgery is to improve a patient's quality of life by increasing their perception of health and their happiness in life, and reducing limitations so that they will ideally be able to participate in life in a more spirited way (Yun et al 1999). Surveys have identified that up to 50% of surgical patients are using CMs, no doubt as a means of achieving the same outcomes. While judicious self-care can offer numerous benefits to the individual, society and the healthcare system, there is clearly the potential for serious adverse outcomes, such as bleeding or drug interactions. The withholding of CMs because of lack of knowledge, fear or misinformation can also be problematic and result in patients being deprived of a therapeutic benefit or in the induction of withdrawal effects. It is not unreasonable to expect that, at some time in the future, unnecessarily

withdrawing CMs or failing to properly advise patients against the use of a potentially harmful product will give rise to serious adverse events resulting in litigation.

Until further clinical testing has been conducted to determine whether the herbal and natural medicines discussed here will adversely affect or beneficially influence the outcome of surgery, a collaborative yet cautious approach is recommended.

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CHAPTER 10
CANCER AND THE SAFETY OF COMPLEMENTARY MEDICINES

Complementary medicine (CM) is commonly used by oncology patients and therefore it is important for healthcare providers to become familiar with this use (Bernstein & Grasso 2001, Ernst & Cassileth 1998, Richardson et al 2000). Typically, cancer patients use vitamins and herbal medicines, spiritual practices and psychosocial and physical therapies. Unfortunately, only 25% of cancer patients using CAM receive information from their conventional healthcare providers and communication between patients and doctors about CM is virtually non-existent (Ernst 2003).

Patients with cancer want access to reliable and authoritative information about CM so that they can discuss benefits and limitations with their healthcare providers and make an informed decision about use. A study of children with cancer has revealed that parents also want information about CM, especially at the beginning of treatment and also in the hospital wards (Molassiotis & Cubbin 2004). Medical and CM practitioners, pharmacists and nurses can play an important role in this regard and do much to guide and support patients using or considering CM. However, in order to provide an informed and rational opinion, healthcare providers require a working knowledge of CM and an awareness of its benefits and potential to cause harm. They also need to keep an open mind, have access to reliable resources and develop collaborative partnerships across several disciplines.

WHY DO PEOPLE WITH CANCER USE COMPLEMENTARY THERAPIES?

People with cancer choose CM as a means of addressing physical and psychosocial issues.

For physical issues, CM is used to provide symptomatic relief from the disease and/or its treatments. This includes addressing symptoms such as pain, nausea and vomiting, fatigue, constipation, weight loss and cachexia, and dyspnoea. It is sometimes used to minimise long-term adverse consequences of treatment such as organ toxicity.

For psychosocial issues, CM offers an avenue for dealing with anxiety, depression, stress and fear. It also provides an opportunity for patient empowerment and can give a sense of control and improve wellbeing.

Patients with cancer who use CM report various positive effects, such as reduced anxiety, stress, nausea, pain and dyspnoea, and improved physical energy, mood, concentration and optimism (Molassiotis & Cubbin 2004, Ponholzer et al 2003). According to a study of children with cancer, CM use was associated with increased confidence, improved pain relief and relaxation (Molassiotis & Cubbin 2004). Importantly, most people with cancer do not expect CM to cure or slow their disease and generally use it as a supportive measure during conventional treatment, chiefly to relieve symptoms and emotional anguish (Ponholzer et al 2003, Rees et al 2000, Richardson et al 2000).

The use of CM is widespread and increasing, partly because of increased access to health information and the growth in research-based evidence supporting the effectiveness of complementary therapies. In addition, CM practitioners tend to have longer consultations than medical practitioners with patients and adopt a holistic approach that focuses on presenting symptoms, the patient's lifestyle and issues that encompass mind, body and spirit. The

Clinical note — Integrative oncology

Integrative medicine may be described as 'practicing medicine in a way that selectively incorporates elements of CM into comprehensive treatment plans alongside solidly orthodox methods of diagnosis and treatment' (Rees & Weil 2001). Integrative oncology (IO) is a subset of integrative medicine. It is a term being increasingly adopted to include complementary medicine (CM), but integrated with conventional cancer treatment, as opposed to being considered a rival or true 'alternative' (Smyth 2006). IO is an evolving evidence-based specialty that focuses on the roles of complementary therapies to increase the effectiveness of conventional cancer treatment programs by improving defined outcomes such as symptom control, quality of life, reduction of patients' distress, rehabilitation and prevention of recurrence (Sagar 2008). The core principles of IO include individualisation, holism, dynamism, synergism and collaboration (Leis et al 2008). CM therapies used in IO include natural medicines (botanicals, vitamins and minerals), nutrition, acupuncture, meditation and other mind-body approaches, music therapy, touch therapies, fitness therapies and others (Sagar 2006).

Integrative medicine in general has grown quickly in the United States and now virtually all major medical centres have departments devoted to integrative patient care, either as true stand-alone centres or departments with a research interest in this area (Boyd 2007). This is particularly true of the major cancer centres, many of which — including Memorial Sloan Kettering Cancer Center, New York; M.D. Anderson Cancer Center, Houston, Texas; Johns Hopkins University, Baltimore, Maryland; Duke University, Durham, North Carolina; and the Dana Farber Cancer Institute, Boston, Massachusetts — have developed integrative cancer programs. In addition, programs such as the Cancer Treatment Centres of America have inpatient and outpatient programs with teams of practitioners, including medical oncologists, surgeons and radiation therapists, as well as credentialled naturopathic doctors, nutritionists, mind–body specialists and other integrative practitioners. Institutions are providing services to patients, exploring the effectiveness gap in their clinical services and are determining efficacy of complementary therapies through randomised controlled trials and, increasingly, mixed method whole systems research (Sagar 2006).

For readers interested in keeping up to date with this evolving area, the journal *Integrative Cancer Therapies* is recommended, as it provides useful research and editorial information about complementary medicine in cancer care.

increased interest in health prevention strategies, such as diet and stress management, are also well catered for by complementary therapists, who see these approaches as essential to good clinical practice.

POOR DISCLOSURE

Although the use of complementary medicines (CMs) is popular among people with cancer, many do not inform their medical doctors that they are using it. This may be because they anticipate disinterest or a negative response or think doctors are unable or unwilling to contribute meaningful information, or because it is perceived as irrelevant to the biomedical treatment course (Adler & Fosket 1999). It is therefore not unusual for patients to be receiving treatment and advice from a variety of practitioners without a central healthcare provider coordinating and supervising care.

Lack of disclosure can give rise to serious problems such as drug interactions and failure to recognise CM-induced adverse effects and withdrawal effects. In oncology, this can have far-reaching consequences. Open and honest communication about CM should be the standard for both patients and clinicians in order to avoid or minimise adverse events and provide an opportunity for patients to express their personal preferences for treatment.

CM IN THE ONCOLOGY SETTING

Despite the increased interest in developing integrative approaches to cancer, many medical oncologists remain sceptical about the value of these modalities. There are several good reasons for oncologists and other staff to take such developments seriously and learn more

about CM instead of dismissing it as eccentric and unproven (Smyth 2006):

- **To enhance mutual respect between patient and doctor.** Oncology patients are using CM and yet all too often they are reluctant to discuss this or even to inform doctors that they are doing so. Mutual respect will help build communication pathways and provide the clinician with an opportunity to ensure that no harm is introduced unwittingly by patients themselves.
- **To encourage research into CM.** One of the major reasons for the medical profession's scepticism of CM is the poor evidence base for many of these treatments. Enquiry, instead of dismissal, will encourage further investigation and research into this area.
- **To increase doctors', pharmacists' and nurses' knowledge of CM.** With ever-increasing access to information and knowledge, patients will continue to challenge their professional advisors on every aspect of cancer management. Complementary medicine approaches will continue to feature strongly in many patients' minds, placing demands on healthcare professionals in the years ahead. One way to help patients is to provide an informed, evidence-based opinion, while acknowledging that, in some cases, randomised studies may not be conducted for years but that other forms of evidence may exist and provide guidance.

BENEFITS OF CM IN ONCOLOGY

A growing number of CM therapies are being subjected to clinical trials to determine their effectiveness and role in cancer treatment. In most instances, CM therapies are being investigated for symptom relief and improvements in quality of life.

A review in the *European Journal of Cancer* illustrates that the weight of evidence to support the use of some complementary approaches in cancer is clearly positive or showing a positive trend (Ernst 2003). According to the review, positive evidence exists for *Allium* spp vegetables (e.g. onions), detoxification, Sho-saiko-to, St John's wort, acupuncture and relaxation, while there is positive trend for green tea, phyto-oestrogens, Gerson diet, *Aloe vera*, melatonin, support group therapy, hypnotherapy, therapeutic touch and enzyme supplements.

Evidence is well established for psychosocial therapies in cancer management, such as hypnosis, music therapy, meditation and stress management, and for acupuncture (Cassileth 1999). For example, there is evidence from randomised trials supporting the value of hypnosis for cancer pain and nausea; relaxation therapy, music therapy and massage for anxiety; and acupuncture for nausea (Vickers & Cassileth 2001). Studies involving people with cancer or cancer survivors report benefits of yoga for stress, anxiety, insomnia and cancer-related symptoms and show it increases quality of life (Bower et al 2005, Cohen et al 2004).

Results from clinical studies and/or experimental models indicate that several other therapies have the potential to reduce drug-induced side effects and toxicities. For example, a Cochrane systematic review that analysed the results of four trials using a Chinese decoction containing the herb astragalus (huang-qi) as an adjunct to chemotherapy concluded that co-administration of the herbal treatment with chemotherapy produced a significant reduction in nausea and vomiting and a decrease in the rate of leucopenia (Taixiang et al 2005). The review also stated that no evidence of harm was identified with use. The herbs ginger and baical skullcap have been found to reduce symptoms of cisplatin-induced nausea in experimental models (Aung et al 2003, Sharma & Gupta 1998, Sharma et al 1997), and animal and human studies suggest long-term carnitine administration may reduce cardiotoxic side effects of adriamycin (Mijares & Lopez 2001, Waldner et al 2006). Additionally, preclinical and clinical studies suggest that anthracycline-induced cardiotoxicity can be prevented by administering coenzyme Q10 during cancer chemotherapy that includes drugs such as doxorubicin and daunorubicin. Studies further suggest that coenzyme Q10 does not interfere with the antineoplastic action of anthracyclines and might even enhance their anticancer effects (Conklin 2005). Many other natural substances such as St Mary's thistle, grapeseed extract, St John's wort, parthenolide (from feverfew) and curcumin show promise in preliminary studies in reducing chemotherapy-induced organ toxicity or other associated adverse effects and are discussed in individual monographs in this book. Research has also been conducted with individual antioxidant vitamins and minerals.

A comprehensive model of cancer care requires that patients take an active role in their healthcare and find partners to work with them during the process. Medical practitioners play a key role; however, many other healthcare providers can augment their

work and help provide patients with holistic care. A number of complementary therapies have proven benefits and are considered safe. These should be made available to patients to increase their sense of wellbeing and improve their quality of life and experience of cancer, its treatments and recovery.

SUPPORTIVE MEASURES

Supportive care is care that helps patients and their families cope with cancer and its treatment, starting from pre-diagnosis, through the process of diagnosis and treatment, to cure, continuing illness or death, and into bereavement. It helps the patient to maximise the benefits of treatment and to live as well as possible with the effects of the disease.

A number of CM therapies and treatments can provide substantial support to people with cancer by providing symptomatic relief, enhanced quality of life and improved sense of wellbeing, without causing harm. They also have important benefits in addition to those derived from their inherent therapeutic effect:

- They actively involve patients and provide a rare opportunity for them to exert control and tend to themselves or to have friends or family members assist them.
- Many CM therapies are time-honoured types of 'supportive care' that have been offered to patients for decades.
- Many are accessible.
- Some work by known mechanisms of action, whereas others may invoke a placebo response, an underutilised mechanism by which distress can be relieved and quality of life enhanced.

The information in Table 10.1 (pp 130–31) is a guide to some of the better known and researched therapies and treatments that may provide supportive benefits for patients. *To promote appropriate and safe use, each individual's characteristics, medication use, general health and overall situation needs to be assessed. Where herbal and nutritional medicines are mentioned, healthcare providers should check for potential interactions with drug therapy.*

CM TO IMPROVE SURVIVAL

Although CM is most often used to treat symptoms and enhance wellbeing, to a lesser extent it is being used as a potential cure for cancer. Examples of some CM treatments that have been used by patients to cure cancer are listed in Tables 10.2 (p 131) and 10.3 (p 132). Some of the listed treatments are currently under investigation and have been subject to in vitro and in vivo studies, whereas other treatments, such as Hoxsey therapy, the Di Bella regimen, shark cartilage and laetrile, are generally considered ineffective. A full review of the available evidence is beyond the scope of this chapter, but further information can be found in the relevant monographs. (Updated information is available at some of the websites listed in Table 10.5, pp 144–5.)

It is interesting to note that approximately two-thirds of commercially available anticancer drugs are derived from or related to natural products, including enzymes, hormones, plants and fungal extracts (Bryant et al 2003). For example, an extract of wild chervil was mentioned in an ancient medical text as a useful salve against tumours, and it is now known that podophyllotoxin, a cytotoxic agent, is present in the *Podophyllum* species of plants. The most recent anticancer products are the taxanes (paclitaxel and docetaxel), which are derived from the yew tree *Taxus baccata*, and the camptothecins (topotecan and irinotecan) from *Camptotheca accuminata*.

RESEARCH APPROACHES AND CONSTRAINTS

The resurgence of medical pluralism has resulted in people with cancer developing their own combinations of biomedical, complementary and self-care strategies. Consequently, the need for a solid knowledge base for the non-surgical, non-radiotherapeutical and non-chemotherapeutical aspects of the treatment experience and their combinations is substantial and will only increase.

Until recently, research efforts in CM and cancer have concentrated mainly on testing a limited number of available treatments using the well-established pharmaceutical randomised controlled trial research model, with tumour size and/or survival as primary outcomes. This has already led to the publication of hundreds of randomised trials in the peer-reviewed literature. While this work is important and will continue, it does not reflect a patient's reasons for seeking CM treatments, which are not primarily tumour reduction, but improved wellbeing and symptom relief.

WHOLE SYSTEMS RESEARCH (WSR)

Cancer care is currently developing into a complicated network of interventions that are delivered at different times and places

TABLE 10.1 CM Therapies Used to Support Cancer Patients

Condition	CM therapy
Anxiety and stress	Acupressure: pressure with fingertips to key locations Aromatherapy: lavender, rosemary, chamomile and marjoram oils are popular; a few drops of oil in the bath, on a pillow, in an oil diffuser or in massage vehicle Meditation and other relaxation techniques: seated or lying down; class or DVD; visualisation and imagery Therapeutic massage: with a trained massage therapist Herbal medicines: brahmi, lemon balm, rhodiola, valerian, passionflower, kava kava, withania, Siberian ginseng; under professional supervision Nutritional supplements: vitamin B complex, SAMe Yoga: class or DVD; breathing exercises can be done by bedridden patients
Backache and muscle aches	Hydrotherapy: e.g. warm bath or spa Nutritional medicine: magnesium and/or calcium supplements, particularly if muscle cramping or muscle tension is a problem Therapeutic massage: with a trained massage therapist Herbal medicines: willowbark, devil's claw tea; or stronger forms under supervision
Depression	Herbal medicine: lemon balm, St John's wort, ginkgo, rhodiola Nutritional medicine: SAMe, fish oils, vitamin B complex Meditation and other relaxation techniques: seated or lying down; class or DVD Yoga: class or DVD; breathing exercises can be done by bedridden patients
Diarrhoea	Probiotics: recolonise bowel with beneficial bacteria Glutamine: symptom relief Herbal medicine: bilberry, chamomile, goldenseal, raspberry leaf tea; or stronger forms under supervision
Dyspepsia	Herbal medicine: dandelion, chamomile, peppermint, cinnamon, ginger, meadowsweet, fenugreek, raspberry leaf teas; or stronger forms under supervision Food supplements: probiotics, colostrum, glutamine
Headaches	Acupressure: pressure with fingertips to key locations Acupuncture Herbal medicine: willow bark, devil's claw Nutritional medicine: magnesium and calcium supplements: particularly if muscle tension is a problem
Nausea and vomiting	Acupuncture Possibly hypnosis Music therapy in combination with antiemetics for stronger effects Herbal medicine: ginger, cinnamon, peppermint tea; or stronger forms under supervision Lime juice taken in water
Pain	Acupuncture: may also increase mobility Biofeedback Herbal medicine: willowbark, ginger, devil's claw tea; or stronger forms under supervision Hypnosis Nutritional supplements: SAMe, fish oil supplements Therapeutic massage: with a trained massage therapist TENS daily for 6+ sessions; may improve fatigue and quality of life, provide acute pain relief and reduce analgesic requirements

TABLE 10.1 CM Therapies Used to Support Cancer Patients *continued*	
Condition	**CM therapy**
Insomnia	Aromatherapy: lavender, rosemary, chamomile and marjoram oils are popular; a few drops of oil in the bath, on a pillow, in an oil diffuser or in massage vehicle Herbal medicine Lemon balm, passionflower, Siberian ginseng, valerian, chamomile tea; or stronger forms under supervision Therapeutic massage: with a trained massage therapist Meditation

TABLE 10.2 Complementary Medicines That have been Used to Improve Cancer Cure Rates	
Complementary medicine	**Comments**
Cat's claw *(Uncaria tormentosa)*	See monograph.
Chapparral	
Coenzyme Q10	There have been several positive case reports.
Curcumin	Attracting a lot of interest from researchers. See monograph.
Essiac tea	Herbal mixture originally formulated by an Ojibwa healer and popularised in the 1920s by a nurse, Rene Caisse. (Essiac is Caisse spelt backwards.) The four main herbs in Essiac tea are burdock root (*Arctium lappa*), Indian rhubarb (*Rheum palmatum*), sheep sorrel (*Rumex acetosella*) and the inner bark of slippery elm (*Ulmus fulva* or *U. rubra*).
Green tea	Attracting a lot of interest from researchers. See monograph.
Laetrile	A single compound isolated from a natural substance (apricot pits and almonds); promoted as 'vitamin B17'.
MGN-3	This is a mushroom and rice bran extract.
Maitake mushroom extract (*Grifola frondosa*)	Maitake D-fraction is used.
Mistletoe extract	Has been subjected to clinical trials in Europe.
Pau d'arco	Used as a tea. Thought to be an old Inca remedy for many illnesses, including cancer. It is made from the bark of an indigenous South American evergreen tree, and its active ingredient, lapachol, has been isolated. See monograph for further information.
PC-SPES	Chinese formulation of eight herbs consisting of isatis (*Isatis indigotica*), either liquorice (*Glycyrrhiza glabra*) or Gan coa (*G. uralensis*), Chinese skullcap (*Scutellaria baicalensis*), reishi (*Ganoderma lucidum*), saw palmetto (*Serenoa repens* or *Sabal serrulata*), Asian ginseng (*Panax ginseng*), denodrantherm (*Denodrantherma morifolium*) and rabdosia (*Rabdosia rubescens*). It is no longer available, as it was also found to contain diethylstilboesterol and warfarin, which increase the risk of adverse effects.
714X	A liquid medicine made from camphor, nitrogen, ammonium salts, sodium chloride, and ethanol, generally given by injection.
Shark cartilage	Thought to have potential owing to antiangiogenic properties. See monograph for further information.

with different intentions. Some interventions are offered by healthcare professionals at an oncology centre; others are offered by CM practitioners; still others, such as special diets, meditation and OTC natural supplements, form part of a patient's individualised package of self-care. These treatment interventions are influenced by psychosocial factors such as the nature of the patient–provider relationship, varying levels of social support, and an individual patient's personality. Ultimately, a patient's outcomes are a result of all components of care, and it is likely that the effect of the whole is greater than the sum of its parts (Verhoef et al 2005).

TABLE 10.3 CM Therapies That have been Used to Improve Cancer Cure Rates

CM therapy	Comments
Chelation therapy	The use of agents to chelate heavy metals.
The Di Bella regimen	Consists of melatonin, bromocriptine, retinoids, and either somatostatin or octreotide.
Electromagnetic therapy	
Fasting and juice therapies	
Hoxsey therapy	Consists of a caustic herbal paste for external cancers or a herbal mixture for 'internal' cancers, combined with laxatives, douches, vitamin supplements and dietary changes; one of oldest alternative cancer treatments in the United States, dating back to the 1920s.
Ozone therapy	

As a result, there is a need to consider whether the current research approaches in clinical cancer care adequately cover the ongoing treatment choices and combinations. One approach developed by CM researchers is whole systems research (WSR), which is proposed as an additional research method for modern systems of care, whether they include complementary medicine or not.

WSR focuses on the multidisciplinary approach taken by patients, rather than adopting a reductionist perspective where all variables remain constant except one that is altered. WSR also focuses more on the individual patient and less on group-averaged results, under the assumption that there will be patient heterogeneity in response and that important information about the healing approach in that heterogeneity may otherwise be missed (Verhoef et al 2005). Integral to WSR is the belief that clinical research should reflect real-world practice and then be used to inform future clinical practice. A mixed-methods approach that holds qualitative and quantitative research methods in equal esteem and captures information about different domains is advocated, because whole systems are complex and no single method can adequately capture the meaning, process and outcomes of these interventions (Verhoef et al 2005).

In summary, WSR is research that:

- encompasses the investigation of both the processes and the outcomes of complex interventions
- includes *all* aspects of any internally consistent approach to treatment (philosophical basis, patients, practitioners, setting of practice and methods/materials)
- acknowledges unique patient, family, community and environmental characteristics and perspectives.

OUTCOMES RESEARCH

Researchers in Canada have determined nine outcome domains relevant to WSR (Fonnebo et al 2007), as follows: physical, psychological, social, spiritual, quality-of-life, holistic, individualised, process and context outcomes. At the same time, validated outcome instruments have been identified to measure these domains as well as gaps where no adequate measures currently exist. Researchers in the UK and at the University of Arizona, USA, have led the way by conceptualising and developing these instruments, some examples of which are Measure Yourself Medical Outcome Profile, Measure Yourself Concerns and Wellbeing, the Patient Enablement Questionnaire, and the Consultation and Relational Empathy Measure (Fonnebo et al 2007).

EXPLORING EXCEPTIONAL PATIENTS

Becoming familiar with patients' individual experiences and collating information to find common themes is one method of identifying therapeutic approaches that show promising results and warrant further clinical research. In a way, this method of data collection is much like the practice of traditional healers of old, who were required to develop excellent observational and history-taking skills to learn more about the benefits and risks of treatments being applied.

This realisation has led to several international initiatives to collect and systematically categorise and review histories of patients who experience an unexpected benefit or spontaneous remission after CM treatments. Several research groups in different countries have initiated studies in this area, either collecting histories from the treatment providers or recruiting case histories mainly from patients themselves (Launso et al 2006). The US National Cancer Institute concentrates on a series of what they designate as 'best cases', whereas in Norway the National Research Centre in Complementary and Alternative Medicine (NAFKAM) includes both 'best' and 'worst' cases in its reviews.

Clinical note — NAFKAM: 'The Exceptional Case History Registry'

This registry is held at the National Research Centre in Complementary and Alternative Medicine (NAFKAM), University of Tromsø, Norway. Its purpose is to establish a database that can contribute to the generation of knowledge about the factors influencing the development of exceptional disease courses after the use of complementary treatment. Researchers carry out a thorough medical evaluation of the case histories that patients send to NAFKAM. At the same time, NAFKAM is interested in collecting information about the experiences and the knowledge of people who themselves define their courses of illness as exceptional. The registry is seen as an important window to patient-based knowledge about disease and treatment courses.

From Galilei 2007

Clinical note — Senate enquiry into services and treatments options for persons with cancer: key recommendations

In June 2005 a report entitled 'The cancer journey: Informing choice' was released as a result of a Senate inquiry conducted earlier in the year (Commonwealth of Australia 2005). The inquiry aimed to investigate the delivery of services and options for treatment for people diagnosed with cancer and to determine how less conventional and complementary cancer treatments can be assessed and judged. With regard to complementary medicine, several important recommendations were made, including a recommendation that the National Health and Medical Research Council provide a dedicated funding stream for research into complementary therapies and medicines and convene an expert working group to identify the research needs relating to complementary therapies, including issues around safety, efficacy and capacity building. The development of collaborative partnerships across disciplines was also advised. The Senate committee also recommended improved provision of authoritative information to patients and health professionals. Importantly, it recommended that where quality of life may be improved by complementary approaches, the means to make such therapies more accessible needs to be reviewed.

LIMITED FUNDING

Despite the enormous popularity of CM, relatively little research has been conducted into the efficacy and safety of its use by people with cancer compared to similar research into conventional medicine. Currently, the majority of research into CM has been conducted in the USA, where a significant effort has been made, with government funding. In 1998 the Office of Cancer Complementary and Alternative Medicine (OCCAM) was established within the National Cancer Institute (NCI) in the United States to coordinate and enhance activities of the NCI in CAM research as it relates to the prevention, diagnosis and treatment of cancer, cancer-related symptoms and side effects of conventional cancer treatments (see http://www.cancer.gov/). Since the establishment of OCCAM, the NCI's research expenditure for CAM has more than quadrupled, from approximately US$28 million for the financial year (FY) 1998 to approximately US$129 million in FY 2004.

In the UK, the National Cancer Research Institute has a complementary therapies clinical studies development group, which is looking at prioritising areas for study and methodological issues. In Australia and New Zealand there is still relatively little government funding for research in this area; however, the establishment of the National Institute of Complementary Medicine (NICM) in 2007 is an important step towards increasing awareness of this need and lobbying government and philanthropic organisations.

ADVERSE REACTIONS AND INTERACTIONS

One area of great concern is the potential for CMs to reduce the efficacy of oncology treatments or increase their adverse effects and toxicity beyond acceptable limits. In conventional drug therapy, interactions are an ongoing concern, although the clinical relevance of these interactions has not always been investigated. In the area of CM, the issue is even more complicated because much remains unknown about the mechanisms of action of many herbal and natural medicines, and relatively little drug interaction research has been conducted.

ADVERSE REACTIONS

Type A and type B adverse reactions are possible with all therapeutic agents, including complementary medicines (see Chapters 7 and 8). Type A effects are the most common and predictable because they are dose-related, generally of mild to moderate intensity, and reversible. Regarding vitamins, minerals and the cancer patient, toxicity concerns mainly relate to vitamin A and the minerals selenium and zinc.

Vitamin A

Cumulative toxicity is possible with daily doses exceeding 100,000 IU, although some adults can experience toxicity signs and symptoms at lower doses. Symptoms tend to resolve within days to weeks. Supplementation should be avoided in chronic renal failure and liver disease, and high-dose vitamin A should be avoided during radiochemotherapy.

Selenium

Cumulative toxicity is possible with daily doses exceeding 1000 micrograms/day. The organic form of selenium found in high-selenium yeast is less toxic and safer than other forms.

Zinc

Single doses of 225–450 mg can induce vomiting. Long-term daily use of 100–150 mg interferes with copper metabolism and can cause hypocuprinaemia, red blood cell microcytosis and neutropenia.

For further information about individual herbs, vitamins and minerals, refer to the relevant monographs.

INTERACTIONS

Cytotoxic anticancer drugs are among the strongest drugs available and tend to have a complex pharmacological profile, narrow therapeutic index, steep dose–toxicity curve and many pharmacokinetic and pharmacodynamic differences both within and between patients (Beijnen & Schellens 2004). Often combinations of medicines are used to address the cancer itself, reduce the associated drug toxicities and provide palliation and symptom relief. As such, polypharmacy is standard practice. Additionally, many cancer patients are elderly and may be taking medicines for comorbid conditions such as cardiovascular disease, and as the number of concomitant medicines increases, so too does the risk of interactions (Blower et al 2005). Age-related changes to renal and hepatic functions and reduced homeostatic reserve are other complicating factors that make the prediction and avoidance of interactions difficult in this population.

As discussed in Chapter 8, there are two main categories of interaction, pharmacodynamic and pharmacokinetic, and a minor category known as physicochemical:

- **Pharmacodynamic** interactions occur when one substance alters the sensitivity or responsiveness of tissues to another. This type of interaction results in additive, synergistic or antagonistic drug effects and is frequently employed in clinical practice to improve patient outcomes. It is of particular concern when medicines used simultaneously have overlapping toxicities.
- **Pharmacokinetic** interactions occur when there is an alteration to the absorption, distribution, metabolism or excretion of a medicine. This interaction results in a change to the amount and persistence of available drug at receptor sites or target tissues. As a result, a change in magnitude of effect or duration of effect can occur, but no change to the type of effect is seen. This interaction is sometimes harnessed to increase serum levels of an expensive medicine without increasing the actual dose.
- **Physicochemical** interactions occur when two substances come into contact and are either physically or chemically incompatible. This type of interaction can take place during the manufacture or administration of medicines and result in the inactivation of one or both medicines.

Regardless of the mechanism involved, three possible outcomes can arise from an interaction: increased therapeutic or adverse effects; decreased therapeutic or adverse effects; a unique response that does not occur when either agent is used alone.

Pharmacodynamic interactions

Antioxidants and chemotherapy

Chemotherapy-related toxicity is a major concern in oncology. The toxicity experienced with the use of chemotherapy agents can be sufficiently severe as to require dosage reduction, delays in treatment and even cessation of potentially effective treatments. Chemotherapy-induced toxicity is also a concern in those patients who are cured or achieve prolonged survival, but experience long-term side effects that reduce their quality of life (Weijl et al 2004).

Much debate has arisen about whether antioxidant supplementation alters the efficacy of cancer chemotherapy. From a theoretical perspective, there is concern that antioxidant supplements have the potential to reduce treatment effectiveness, especially if oxidative mechanisms play a role in producing cytotoxic effects. Drugs with mechanisms of action which include free radical generation include, but are not limited to, alkylating agents (e.g. melphalan, cyclophosphamide), anthracyclines (e.g. doxorubicin, epirubicin), podophyllin derivatives (e.g. etoposide), platinum coordination complexes (e.g. cisplatin, carboplatin) and camptothecins (e.g. topotecan, irinotecan) (Labriola & Livingston 1999). Unfortunately, free radicals produced during the course of treatment are also a major source of serious side effects. For example, cisplatin and other platinum-induced toxicities include nephrotoxicity, ototoxicity and peripheral neuropathy, while doxorubicin and other anthracyclines often cause cardiotoxicity (Block et al 2007). There are other chemotherapy drugs that are thought to be less reliant on free radical production as a mechanism of action, such as plant-derived agents (e.g. vinca alkaloids and taxanes), antimetabolites (e.g. methotrexate, fluorouracil, cytarabine) and hormonal agents (Labriola & Livingston 1999).

Attempting to characterise chemotherapeutic compounds solely in this manner oversimplifies the issue, as most effective chemotherapeutic agents are multi-mechanistic and their relative ability to generate free radicals is not only dose-dependent but also dependent on the localisation and metabolism of the drug within specific tissues (Block et al 2007). Importantly, these cytotoxic drugs tend to have additional mechanisms of action that are not reliant on free radical generation, enabling them to target cells in a number of different ways.

Similarly, antioxidants have multiple mechanisms of action and, depending on their use and dosage, have the potential to serve as free radical molecules themselves.

Currently, clinical evidence is generally lacking to support concerns that antioxidant supplementation given concurrently with reactive-oxygen-species-(ROS)-generating chemotherapy will diminish the efficacy of treatment; however, the area remains underresearched and definitive evidence is still not available.

A historical perspective The concept of administering antioxidant vitamins in cancer probably arose in the 1970s as a result of publications by Linus Pauling and Ewan Cameron. In one of their early papers entitled 'Orthomolecular treatment of cancer — the role of vitamin C in host defence', it is proposed that cancer treatment must be multidisciplinary and include all that medicine and surgery has to offer and also treatments that maximise the individual patient's resistance to cancer (Cameron & Pauling 1974). The phrase 'orthomolecular treatment' was described as a means of enhancing patients' responses, achieved by manipulating certain biochemical reactions. High-dose vitamin C supplementation was chosen as a good candidate to enhance host resistance, based on theoretical considerations, preliminary studies and the observation that many cancer patients had depleted vitamin C levels.

Cameron and Pauling went on to publish two controlled retrospective studies in 1976 and 1978 that showed that the mean survival times were, respectively, more than four and three times as great for the ascorbate subjects as for the controls with the use of intravenously and orally administered high-dose vitamin C (Verrax & Buc Calderon 2008). Pauling and collaborators were convinced that high doses of ascorbate would increase the formation of collagen, leading to tumour encapsulation. Rapidly, several criticisms were raised about the design of the Pauling/Cameron studies since they were not randomised or placebo-controlled and had other methodological weaknesses. In an attempt to either duplicate or refute the amazing results obtained by Cameron and Pauling, the Mayo Clinic initiated different controlled double-blind studies, but these did not find that treatment was effective against advanced malignant disease.

In the last 30 years, our knowledge of the pharmacokinetics and pharmacodynamics of ascorbic acid has increased and provides the rationale to support its re-evaluation as adjuvant treatment for cancer patients. Indeed, ascorbic acid is cytotoxic against a wide variety of cancer cells but presents a low toxicity towards normal cells, which could lead to the consideration of ascorbate as an interesting anticancer agent (Verrax & Buc Calderon 2008).

The evidence today A number of comprehensive reviews in the peer-reviewed literature have assessed the effects of combined

antioxidant and chemotherapy usage on different outcomes such as side-effect reduction, reduced toxicity and, to a lesser extent, survival. While there are some promising findings, particularly indicating that antioxidants reduce chemotherapy-induced toxicity, definitive conclusions about safety and efficacy cannot yet be drawn because of the variations in study design, intervention protocols, eligibility criteria, statistical power, timing of the observation or intervention, malignancy type and anticancer regimens.

Block et al (2007) evaluated data from 19 randomised controlled trials (n = 1554 patients) in which studies measured survival and/or treatment-response levels of patients who were given antioxidants concurrently with chemotherapy in order to determine if the antioxidants enhanced or interfered with the efficacy of the chemotherapy. Reviewers found no evidence to support concerns that antioxidant supplementation diminished the efficacy of chemotherapy in study populations comprising mostly advanced or relapsed patients; overall, studies showed a positive trend in the survival and response rates for the groups receiving the antioxidants. Although these results are certainly encouraging, only four studies provided adequate statistical data to support the positive conclusion made by Block et al.

Statistics were more robust to support the conclusion that antioxidant therapy reduced chemotherapy-induced toxicity. Seventeen studies reported on toxicity; 15 of these showed similar or reduced toxicities in the antioxidant group compared to controls; only one study reported significantly greater general toxicity, although the result was somewhat expected owing to the well-documented toxicities of high-dose vitamin A. One other study reported that 2 out of 8 measured toxicities were non-significantly higher; however, the authors reported difficulty in interpretation because of poor patient compliance in the antioxidant group. More specifically, with regard to neurotoxicity, all 11 studies found antioxidant supplementation led to similar or less neurotoxicity compared to controls.

The comprehensive review looked at antioxidants with different mechanisms, such as free-radical scavengers that act as reducers or that break lipid chains (melatonin, *N*-acetylcysteine [NAC], Vitamin E, glutathione [GSH], beta-carotene and vitamin C), metal chelators (Vitamin C, epigallocatechin gallate from green tea [EGCG]), cellular protectors (vitamins A, C, E and melatonin), those that target and repair DNA aberrations (EGCG) and antioxidant enzymes created by combining with a protein to form selenoproteins (selenium, GSH). Only studies in which cancer patients were undergoing chemotherapy at the same time were included, as were all types of cancer and various chemotherapies that utilised the reactive oxygen species mechanism.

Some recently published reviews have come to a similar conclusion (Simone & Simone 2008, Simone et al 2007). The authors evaluated 280 peer-reviewed in vitro and in vivo studies, including 50 human studies involving 8,521 patients (5,081 of whom were given nutrients) and concluded that studies have consistently shown that antioxidants do not interfere with therapeutic modalities for cancer. Furthermore, they contend that non-prescription antioxidants and other nutrients enhance the killing of therapeutic modalities for cancer, decrease their side effects and protect normal tissue. In 15 human studies, 3,738 patients who took non-prescription antioxidants and other nutrients actually had increased survival.

In contrast, a 2008 review (Lawenda et al 2008) advises against the concurrent use of antioxidants during chemotherapy because of the possibility of tumor protection and reduced survival. The authors identified 16 randomised clinical trials that studied the concurrent use of antioxidant supplements and chemotherapy; six of those trials included a placebo control. Although no decrements in tumor response rates or survival rates were observed in the studies that reported response data, it was reported that none of the studies were sufficiently powered to evaluate these endpoints.

Theories explaining the observed improvement in survival and/or treatment response reported in some clinical studies with antioxidant supplementation have been offered (Conklin 2004, Block et al 2007). It is suggested that oxidative stress can slow the cell-cycle progression of cancer cells, which can interfere with the ability of anticancer agents to kill cells, and that the formation of reactive oxygen species (ROS), such as aldehydes, can inhibit drug-induced apoptosis and further diminish treatment effects. It is further proposed that the use of antioxidant agents during chemotherapy could enhance treatment effectiveness by decreasing this unwanted effect of ROS generation. In the 2007 review by Block et al, it was suggested that antioxidant therapy

reduced free-radical-induced damage to normal tissues, leaving non-oxidative cytotoxic mechanisms unaffected. In this way, patients experienced fewer dose-limiting toxicities, so that more of them could successfully complete prescribed regimens.

Cisplatin and antioxidants

One of the most important drugs used for the treatment of a wide range of solid tumours is cisplatin, but it induces numerous toxicities that are mainly caused by the formation of free radicals, leading to oxidative organ damage. Long-term side effects of treatment include nephrotoxicity, loss of high-tone hearing and peripheral neuropathy. As a strategy to reduce oxidative damage and drug-induced toxicities, antioxidants (nutritional and herbal) have been investigated in both animals and humans, with some studies showing amelioration or prevention of some side effects and possibly increased treatment effectiveness (Ali & Al Moundhri 2006, Lamson & Brignall 1999, Ohkawa et al 1988, Seifried et al 2003).

Neurotoxic protection The neurotoxicity of chemotherapy depends not only on the anticancer agent used, the cumulative dose and the delivery method, but also on the capacity of the nerve to cope with the nerve-damaging process. The sensory and motor symptoms and signs of neurotoxicity are disabling, and have a significant impact on the quality of life of cancer patients. Moreover, the risk of cumulative toxicity may limit the use of highly effective chemotherapeutic agents. Therefore, prophylaxis and treatment of peripheral neurotoxicity secondary to chemotherapy are major clinical issues (De 2007).

Experimental and clinical studies have been conducted to investigate whether naturally derived antioxidants prevent cisplatin-induced neurotoxicity, overall producing promising results. In a recent review of four trials, for example, the combination of vitamin E with cisplatin was shown in all trials to reduce the incidence of chemotherapy-induced peripheral neuropathy (Wolf et al 2008). While no data was included on the long-term survival of the patients involved, numerous studies have been undertaken that failed to show a detrimental effect from combining vitamin E with chemotherapy. For instance, Argyriou et al conducted a randomised, open label trial with blind assessment to investigate whether vitamin E supplementation (600 mg/day) has a neuroprotective effect in chemotherapy-induced peripheral nerve damage (Argyriou et al 2005). Thirty-one patients with cancer treated with six courses of cumulative cisplatin, paclitaxel or their combination regimens were randomly assigned to be controls receiving standard care, or to receive oral vitamin E at a daily dose of 600 mg/day during chemotherapy and for 3 months after its cessation. The incidence of neurotoxicity differed between the two groups, occurring in 25% patients taking vitamin E and 73% of controls ($P = 0.019$).

In several experimental settings, the prophylactic administration of acetyl-L-carnitine (ALC), the acetyl ester of L-carnitine, prevented the occurrence of peripheral neurotoxicity commonly induced by chemotherapeutic agents and further promoted recovery of nerve function (De 2007). Recent in vitro research suggests alpha-lipoic acid exerts neuroprotective effects against cisplatin-induced neurotoxicity in sensory neurons by protecting against mitochondrial toxicity, which is an early common event in cisplatin-induced neurotoxicity (Melli et al 2008).

Nephrotoxic protection Many different agents have been shown to ameliorate experimental cisplatin-induced nephrotoxicity including antioxidants (e.g. melatonin, vitamin E, selenium, St John's wort, capsaicin, garlic powder, spirulina, tetramethylpyrazine, a major constituent of the Chinese herb *Ligusticum wallichi*, and many others) and modulators of nitric oxide (e.g. zinc histidine complex, L-arginine) (Ali & Al Moundhri 2006, Khan et al 2006, Mohan et al 2006, Razo-Rodriguez et al 2008, Saleh & El-Demerash 2005, Shimeda et al 2005). Only few of these agents have been tested in humans.

A randomised study using 4000 micrograms/day of selenium (as seleno-kappacarrageenan), given 4 days before to 4 days after treatment with cisplatin, found that it effectively reduced drug-induced nephrotoxicity and bone-marrow suppression (Hu et al 1997). Another randomised study that tested oral vitamin E (300 mg/day), given before treatment and continued for 3 months post-treatment, showed it significantly reduced the incidence and severity of neurotoxicity associated with cisplatin (Pace et al 2003).

Alternatively, combination therapy with vitamins C and E and selenium in 48 subjects failed to exert protective effects against cisplatin-induced nephrotoxicity and ototoxicity, according to a double-blind study (Weijl et al 2004). The doses used in that study were 1000 mg vitamin C (as L-ascorbic acid), 400 mg

vitamin E (as DL-alpha-tocopherol-acetate) and 100 micrograms selenium (as sodium selenite), which was taken as a milky beverage 7 days before the onset of chemotherapy and continued until 3 weeks after cessation of therapy. Unfortunately, the interpretation of the results is difficult, as the study was hampered by very poor patient compliance, with only 36% of the intervention patients drinking the antioxidant-enhanced beverage for the duration of the test period. Additionally, the study has been criticised for using insufficient doses of antioxidants and, although supplementation led to a marked increase in plasma antioxidant levels before cisplatin treatment, enhanced levels were not maintained during chemotherapy. Clearly, further investigation is required.

Antioxidants and radiation therapy

Until recently, research attention has focused primarily on the interaction of antioxidants with chemotherapy, and relatively little attention has been paid to the interaction of antioxidants with radiotherapy. In general, oncologists take the view that antioxidants diminish the effectiveness of radiation therapy; however, there is great variation in the degree of concern over this issue.

Reviews by Moss (2007) and Lawenda et al (2008) provide summaries of the available evidence to determine whether antioxidants interfere with radiation therapy. The different conclusions drawn by the two reviews clearly indicate that the issue of safety in this population is far from decided.

In the literature, published studies have reported on the use of alpha-tocopherol for the amelioration of radiation-induced mucositis; pentoxifylline and vitamin E to correct the adverse effects of radiotherapy; melatonin alongside radiotherapy in the treatment of brain cancer; retinol palmitate as a treatment for radiation-induced proctopathy; a combination of antioxidants (and other naturopathic treatments) and external beam radiation therapy as definitive treatment for prostate cancer; and the use of synthetic antioxidants, amifostine, dexrazoxane, and mesna as radioprotectants. Moss (2007) concluded that, with few exceptions, most of the studies draw positive conclusions about the interaction of antioxidants and radiotherapy.

In contrast, Lawenda et al (2008) came to a different conclusion and advised against the concurrent use of antioxidant supplements. Five randomised clinical studies are reported that investigated the use of high-dose vitamin E (400–600 mg/day or 400 IU/day), high-dose beta-carotene (30 mg/day) or melatonin (20 mg/night) in patients with head and neck cancers, non-small-cell lung cancer, brain metastases or glioblastoma multiforme who were receiving radiotherapy. Two of these studies produced negative findings. The most concerning was that generated by Bairati et al (2005) who conducted a randomised, double-blind, placebo-controlled study involving 540 head and neck cancer patients treated with radiation therapy. Patients receiving supplementation with alpha-tocopherol (400 IU/day) and beta-carotene (30 mg/day) administered during radiation therapy and for 3 years thereafter tended to have less severe acute adverse effects during radiation therapy; however, the rate of local recurrence of the head and neck tumour tended to be higher in the supplement arm of the trial. Subgroup analysis published later found that interactions between antioxidant supplementation and cigarette smoking during radiation therapy were associated with an increase in both disease recurrence and cancer-specific mortality, whereas no increase in either of these outcome measures was observed for the non-smokers (Meyer et al 2008).

Lawenda et al (2008) point out that it is important to distinguish between high-dose and relatively low-dose antioxidant supplementation and the variations in antioxidant classes, because these differences may substantially define the efficacy and safety profiles of specific antioxidant supplements as therapy for cancer patients receiving selected chemotherapy agents or radiation therapy. Conklin, from the University of California, Los Angeles (UCLA) puts forward the theory that while radiation kills cells by generating high levels of free radicals, the effect is most successful in well-oxygenated tissues (Moss 2007). Tumours, particularly large ones, are often hypoxic at their core, thereby diminishing the effectiveness of radiation. He further suggests that the degree of free radical generation is proportional to the oxygen tension in the tissue, and with improved blood flow, resulting from relatively low-to-moderate doses of antioxidants, improved neoplastic activity may be seen. Conklin also makes the point that the dose of antioxidant supplementation must be sufficiently low to avoid the risk of diminishing treatment efficacy.

Increased risk of bruising and bleeding

A number of commonly used herbs and natural supplements demonstrate antiplatelet activity and have the potential to increase the incidence of bruising and/or bleeding when taken in sufficient dosage. This is of particular concern for patients undergoing major surgery who are taking anticoagulants or conventional antiplatelet agents. A list of these substances is given in Chapter 9.

Hormonally responsive tumours

Hormonal agents are used when a neoplasm is sensitive to hormonal growth controls in the body; for example, prostate cancer is stimulated by male androgens and breast cancer by oestrogen. Chemical treatment may consist of anti-androgens, anti-oestrogens and/or cytotoxic agents. Many constituents in herbs and everyday foodstuffs can theoretically stimulate or inhibit tumour growth or interact with hormonal treatments. The flavonoid group of naturally occurring chemicals provides a good example.

Flavonoids are polyphenolic compounds that are widely found in vegetables, nuts, fruits, beverages (e.g. coffee, tea and red wine) and medicinal herbs such as St Mary's thistle and St John's wort. They exert a wide range of biochemical and pharmacological actions and have been the focus of much interest, especially with regard to their cancer-protective activities, which are attributed to free radical scavenging, modification of the enzymes that activate or detoxify carcinogens, and inhibiting the induction of the transcription factor activator protein-1 activity by tumour promoters (Moon et al 2006).

Some of these compounds have been found to decrease oestrogen biosynthesis; for example, the flavones chrysin and baicalin, the flavonones (naringenin) and isoflavones (genistein, biochanin A) (Moon et al 2006). This is achieved by inhibiting the activity of aromatase (cytochrome P19) and could theoretically have a use in breast and prostate cancer (Kao et al 1998). Additionally, some flavonoids, such as soy isoflavones, can bind to oestrogen receptors and might slow down cell proliferation as a consequence (Wood et al 2006). Unfortunately, the bioavailability of many dietary flavonoids tends to be low, so effects seen in vitro do not necessarily reflect in vivo responses; however, this may not be true for herbal preparations or functional foods with concentrated flavonoid levels that may achieve much higher plasma concentrations.

Soy and isoflavones Dietary soy isoflavones have attracted a lot of attention as potential cancer-protective agents, chiefly because of observations that high consumption in Asian diets has been correlated with lower incidence of prostate and breast cancers. Currently the data available is contradictory and it is still unclear under what conditions soy isoflavones have cancer protective effects, if at all.

The potential for soy isoflavones to either enhance or antagonise the effects of anticancer medicines such as tamoxifen has also been investigated in several experimental models. Most studies have focused on genistein, because of its relatively strong binding (in comparison to daidzein) to the alpha- and beta-oestrogen receptors and its oestrogenic/anti-oestrogenic activities, which are stronger than those of other isoflavones (Constantinou et al 2005). Some studies have raised the possibility that genistein could compete with tamoxifen for oestrogen receptors and thereby decrease the drug's efficacy, an observation seen in two experimental models (Constantinou et al 2005, Ju et al 2002). Alternatively, research conducted with daidzein has produced positive results and showed that it enhanced the effect of tamoxifen against mammary carcinogenesis in the rat model (Constantinou et al 2005). In fact, the combination of tamoxifen/daidzein was more effective than tamoxifen alone for reducing tumour burden, incidence and multiplicity, as well as increasing tumour latency. When these results are taken together, it appears that although the isoflavone genistein may have a deleterious effect when combined with tamoxifen, the use of soybeans in combination with tamoxifen is not necessarily dangerous and beneficial effects may even be possible.

Drug inactivation — chemical incompatibility

Predicting interactions between natural products and chemotherapeutic drugs is difficult and occasionally unexpected findings come up. The following case highlights the challenges in making interaction predictions in the area of IO and provides a good example of drug inactivation caused by a natural compound.

In recent years, chemopreventative and chemotherapeutic effects of green tea have been reported in different malignancies and have become well known. Epigallocatechin-3-gallate (EGCG), the most abundant and biologically active polyphenol in green tea, selectively inhibits cell growth and induces

apoptosis in cancer cells without adversely affecting normal cells. The antitumour effects of EGCG include inhibition of angiogenesis, modulation of growth-factor-mediated proliferation, suppression of oxidative damage, induction of apoptosis and cell-cycle arrest. As a result, it has become a popular beverage amongst people with cancer or at risk of cancer.

In 2006, Shammas et al (2006) reported that EGCG demonstrated potent and specific antimyeloma activity in experimental models, thereby suggesting it could have a role in chemoprevention and possibly treatment of multiple myeloma. As a result, a few years later EGCG was tested in vitro and in vivo to investigate whether combining it with the proteasome inhibitor bortezomib (BZM), commonly used in the treatment of multiple myeloma, would result in an increase in the drug's antitumour activity (Golden et al 2009). The results were surprising, as green tea extract almost completely blocked the effects of BZM both in vitro and in vivo.

Upon further investigation, it was found the interaction was due to a 1,2-benzene diol moiety contained in some of the green tea constituents, particularly the epigallocatechin-gallate (EGCG) which formed stable covalent bonds with the boronic acid moiety of BZM. The formation of the new boronate product resulted in little to none of the proteasome-blocking effect usually observed for BZM, thereby neutralising the cytotoxic activity of BZM. The pronounced antagonistic function of EGCG was evident only with boronic acid-based proteasome inhibitors (bortezomib, MG-262, PS-IX), but not with several non-boronic acid proteasome inhibitors (MG-132, PS-I, nelfinavir).

Although the in vivo component of this study was carried out in mice, the evidence is compelling and strongly suggests that in current practice the combination of BZM and green tea should be avoided until proven safe in clinical studies. It is important to note that this interaction was not based on an antioxidant/free radical mechanism and hence cannot be extrapolated to other antioxidants based solely on their free radical scavenging activity. Whether other agents containing the 1,2-benzene diol moiety also interact with boronic acid-based proteasome inhibitors in the same way is unknown, but it would be prudent to avoid concurrent use until safety is established. Some components containing the 1,2-benzene diol moiety found in the diet and as constituents in several herbal medicines include quercetin and myricetin, which have previously been shown to inhibit BZM in vitro (Liu et al 2008).

Pharmacokinetic interactions

Pharmacokinetic interactions often involve metabolising enzymes or drug transporters that have great significance in chemotherapy. Cytochrome enzymes (CYP) and drug transporters in the intestinal epithelium affect the bioavailability of many oral chemotherapy agents and can induce multidrug resistance.

P-glycoprotein

One mechanism responsible for multidrug resistance is overexpression of the adenosine-triphosphate(ATP)-binding cassette-containing family of proteins such as P-glycoprotein (P-gp), which has a counter-transport role and actively forces substrates out of cells. These proteins are expressed in both healthy cells, such as the blood–brain barrier, and resistant tumour cells, and act as a barrier. Of significance, they are highly expressed in the lumen of the gut and can substantially impede the oral uptake of several anticancer medicines (Beijnen & Schellens 2004). Examples of anticancer medicines that are P-gp substrates are:

- daunorubicin
- docetaxel
- doxorubicin
- paclitaxel
- taxol
- tacrolimus
- vinblastine
- vincristine.

An interaction will occur when a substrate is co-administered with another substance that alters the expression of the relevant counter-transport protein. In regards to P-gp, expression can be altered by a number of factors such as common foods, herbs and pharmaceutical medicines. A promising strategy is to use P-gp inhibitors to increase drug bioavailability and reverse multidrug resistance in tumours; for example, the use of oral cyclosporine and paclitaxel has proved successful in a phase II study of people with advanced non-small-cell lung cancer (Kruijtzer et al 2002). Alternatively, P-gp inducers can have the opposite effect and reduce the bioavailability of P-gp substrates and increase drug resistance: they should be avoided when medicines that are P-gp substrates are administered.

Herbal and natural medicines affecting P-gp The influence of herbal and natural medicines on P-gp expression has only recently been investigated, so much is still unknown and speculative. To date, most research has centred on St John's wort (*Hypericum perforatum*), which has significant P-gp induction effects, as demonstrated in clinical testing (Durr et al 2000). Studies have found that, after 16 days of continual use, P-gp expression can increase 4.2-fold. The hyperforin constituent is responsible for the induction effect, which is achieved by activation of the pregnane X receptor (Moore 2000). In Europe, some manufacturers have produced low-hyperforin-containing herbal products, which may not have the same effect. Besides St John's wort, the isoflavone genistein is reported in other studies to inhibit P-gp-mediated drug transport (Castro & Altenberg 1997).

Alternatively, rosemary extract acts as a P-gp inhibitor. According to an in vitro study, multidrug-resistant mammary tumour cells treated with rosemary extract produced an increase in intracellular concentrations of doxorubicin and vinblastine, both of which are P-gp substrates (Plouzek et al 1999), and the same effects were not seen in cells that lack P-gp expression. More recently, an in vitro study identified that bitter melon (*Momordica charantia*) leaf extract exhibited dose-dependent P-gp inhibition, which resulted in intracellular vinblastine accumulation (Limtrakul et al 2004). The effect was not seen for the fruit. Many other natural substances affect P-gp and have potential as useful adjuncts in the chemotherapeutic treatment of cancer.

Cytochromes and metabolism

Many drugs undergo two phases of metabolism: phase I, or functionalisation reactions, and phase II, or conjugation reactions. Many medicines, nutrients, environmental toxins and endogenous substances undergo metabolism by the CYP P450 system during phase I metabolism. As a result, an active substance can be converted into an inactive, less active, more active or toxic metabolite, or an inactive prodrug can be converted into an active one. Although there are over 50 enzymes in the CYP system, the most important for drug metabolism are CYP1A2, 2D6 and 3A4. In particular, CYP3A4 is involved in the metabolism of many anticancer medicines, some examples of which are the oxazaphosphorines (cyclophosphamide, ifosfamide) and the taxanes (paclitaxel, docetaxel) (Beijnen & Schellens 2004) (see also Table 10.4).

Interactions occur when CYP substrates and inducers or inhibitors are taken at the same time.

Herbal and natural supplements affecting CYP enzymes Many factors can interfere with CYP activity, such as the ingestion of foreign compounds (e.g. environmental contaminants) or of certain constituents found in food, beverages, herbs or medicines. Of the herbal medicines commonly available, most research has been conducted with St John's wort, which significantly induces CYP enzymes, particularly CYP3A4 with long-term administration (Durr et al 2000, Roby et al 2000, Ruschitzka et al 2000). Once again, these effects are attributed to the interaction between hyperforin and the pregnane X receptor, which regulates expression of CYP3A4 mono-oxygenase. In this way, hyperforin increases the availability of CYP3A4, resulting in enzyme induction (Moore et al 2000). Clinically, this means that serum levels of those medicines that are CYP3A4 substrates will be reduced, which can reduce drug effectiveness and possibly induce therapeutic failure.

In recent years a growing number of other herbal medicines have been subjected to interaction studies and investigated for effects on CYP isoenzymes and transporter proteins, using new in vitro and in vivo techniques. The evidence from these tests suggests that several other herbal medicines have the potential to

TABLE 10.4 Cytochrome Enzymes Involved in the Metabolism of Chemotherapeutic Drugs

Cytochrome enzyme	Chemotherapeutic drug
CYP 1A1, 1A2	dacarbazine
CYP 2A6	cyclophosphamide, ifosfamide, tegafur
CYP 2B6	cyclophosphamide, ifosfamide
CYP 2C8	cyclophosphamide, ifosfamide, paclitaxel
CYP 2C9	cyclophosphamide, ifosfamide
CYP 2C19	teniposide
CYP 2D6	tamoxifen, doxorubicin, vinblastine
CYP 2E1	dacarbazine
CYP 3A4	teniposide, etoposide, epipodophyllotoxin, cyclophosphamide, ifosfamide, vindesine, vinblastine, vincristine, vinorelbine, paclitaxel, docetaxel, irinotecan, tamoxifen
CYP 3A5	etoposide, tipifarnib

affect drug absorption and/or metabolism. However, readers are advised that translation of in vitro data to clinical practice is problematic and imperfect, and in vivo testing is required before an interaction prediction can be made.

For example, silymarin, the active constituent group from St Mary's thistle, significantly decreases CYP3A4 activity in primary cultures of human hepatocytes; however, four clinical studies have found no clinically significant effects in vivo (Gurley et al 2004, DiCenzo et al 2003, Leber & Knauff 1976, Piscitelli et al 2002). The daily doses of silymarin used in the clinical studies ranged from 210 mg to 480 mg.

ELIMINATION

Although most anticancer medicines are eliminated though metabolism, some, such as the platinum compounds and methotrexate, are eliminated mainly by the kidneys through glomerular filtration and active tubular secretion (Beijnen & Schellens 2004). Urinary excretion can be altered by substances that affect urinary pH, which will affect renal tubular reabsorption. One substance sometimes used by cancer patients is ascorbic acid. Although low-dose ascorbic acid is unlikely to cause detrimental effects, high doses that acidify the urine can affect the excretion of drug metabolites, which precipitate in the renal tubules at low pH. As a result, there has been a theoretical concern that high-dose vitamin C could precipitate methotrexate. A study by Sketris et al (1984) investigated the proposed interaction and found that it does not appear to be clinically significant; however, caution is still advised.

CLINICAL IMPLICATIONS OF INTEGRATIVE MEDICINE

People with cancer expect their healthcare providers to work with them to achieve adequate symptom relief, improved quality of life and a cure. In order for this to be achieved, a holistic approach that combines several different disciplines is best.

Although the role of some forms of CM in cancer is still unclear, there is evidence to support the use of several therapies and treatments. When therapies are considered safe and provide a supportive role in cancer, either for symptom relief or improvements in wellbeing and quality of life, they should be made available and become a part of standard protocol. This requires access to reliable information and a collaborative partnership with a variety of healthcare providers based on mutual respect and open communication.

SHARED DECISION MAKING

A wide range of patient- and physician-related factors affect clinical decision making and subsequent use or disuse of CM.

1. General safety issues

Patient safety is paramount. Medicinal CM treatments (CMs) can pose a risk to patients via several mechanisms:

- Interference with blood clotting. Cancer patients often have low platelets at various points throughout their treatment, either as a direct result of the cancer itself, or as a temporary side effect from the chemotherapy or radiotherapy. CMs that significantly inhibit blood clotting will increase the risk of haemorrhage.
- Interactions with conventional chemotherapy drugs or radiation therapy resulting in diminished therapeutic effect.
- Interactions with conventional chemotherapy drugs or radiation therapy resulting in increased toxicity and/or other side effects.

Product quality is particularly important to assess in this population. For example, products contaminated with microorganisms can have serious consequences for immunosuppressed patients who have limited ability to mount an immune response.

Such concerns obviously do not relate to non-medicinal CM therapies such as massage and meditation, which may provide significant improvement to patients' wellbeing and quality of life during treatment. In this regard, finding an appropriately trained and credentialled practitioner with experience in treating cancer patients provides some safeguard against possible harm.

2. Availability of credible information sources

Credible, accurate and timely information is required for both patients and healthcare providers in order for evidence-based patient-centred care to occur.

Asking patients about their interest in and use of CM therapies is essential for good practice. Understanding their reasons for use and the information sources to which they have referred when making such decisions is also important. For many patients, family and friends are the main sources of information;

others use CM practitioners, the internet, books and magazines.

When discussing the reliability of the information, some points to guide the patient may include:

- Was the internet site used an officially recognised and registered site? Is it frequently updated and what are the credentials of the authors providing content for the site?
- Was the internet site supporting a profit-driven enterprise? Was information in advertorial style, rather than independently written?
- If CM practitioners were consulted, are they registered or accredited with a professional association? What is their training and experience? Credentials?

Healthcare providers should ensure that they:

- have access to current, credible and relevant information sources
- have effective information-seeking skills to locate information from databases and other resources
- are able to critically evaluate the information retrieved
- have a network of reliable CM practitioners who can provide additional information about treatments when necessary, as sometimes the peer-reviewed medical press has little useful information about some CM treatments.

3. Evidence of efficacy and safety

Evidence-based patient-centred care means amassing and evaluating the best available evidence and involving patients in a shared decision making process that takes into account their individual circumstances and wishes.

The emerging picture shows that the evidence base is greater for some CM therapies than others, and there is an urgent need for more research from a variety of perspectives and methodological approaches. Peer-reviewed journals provide a good starting point for gathering evidence, and frequently updated databases written by people expert in CM are also useful. It is important to note what evidence exists, but also what is missing and remains unknown. Importantly, keep in mind that *a lack of evidence is not necessarily evidence of a lack of effectiveness.* It is likely that some CM treatments being used by patients are effective, but have not yet been subjected to clinical trials. Table 10.5 gives a list of useful internet information sources.

When reviewing the evidence, look for:

- in vitro tests and studies with animal models that provide information about mechanisms, pharmacokinetic influences and the potential effects in humans, although they are not definitive
- clinical studies to provide more relevant information — consider the patient group involved, intent of treatment, interventions used (dose, form, time frames, administration method, type of extract), what other medications were also used (where relevant) and outcomes measured
- up-to-date, comprehensive reviews of the literature.

4. Intent behind using CM treatment

CM therapies are generally used as adjuncts to conventional treatments and, in the case of cancer, to improve quality of life, address symptoms and reduce toxic side effects. Far less common is their use as a potentially curative treatment. The decision to use CM therapies for symptom relief requires different consideration from using CM for curative purposes or as an alternative to conventional care.

5. Severity of disease

The use of CM by people with readily curable cancers is often viewed differently to its use by people with difficult-to-treat cancers or by palliative patients.

Highly curable cancers

When conventional treatments have a high cure rate, then concomitant use of less proven treatments should be avoided unless there is clear evidence that it will not diminish outcomes. For example, testicular cancer currently has a 99% 5-year survival rate when treated aggressively with chemotherapy (see http://www.cancervic.org.au/about-our-research/cancer-statistics). The chemotherapy used for this type of cancer commonly involves cisplatin. Although some clinical studies indicate that concurrent use of antioxidants is likely to be safe, until definitive evidence becomes available it is prudent to avoid use during curative treatment.

If the patient understands the risks associated with the use of complementary medicinal agents during curative treatment, and voluntarily decides to use CM treatment, a compromise may sometimes be reached. It is reasonable to suggest the patient takes CM treatment in between treatment cycles, but abstains for a certain time period before, during and after curative treatment to minimise the risk of drug interactions. The washout period between treatments will depend on the pharmacokinetics of the agents being used.

TABLE 10.5 Useful Web-Based Information Sources

Information source and URL	Description
National Cancer Institute (USA) http://cancer.gov	The National Cancer Institute (NCI) is a component of the National Institutes of Health (NIH), one of eight agencies that compose the Public Health Service (PHS) in the Department of Health and Human Services (DHHS). The NCI, established under the National Cancer Act of 1937, is the Federal Government's principal agency for cancer research and training. The website includes cancer topics, clinical trials, cancer statistics, research and funding, and cancer-related news.
Office of Cancer Complementary and Alternative Medicine http://www3.cancer.gov/occam	The Office of Cancer Complementary and Alternative Medicine (OCCAM) was established in October 1998 to coordinate and enhance the activities of the National Cancer Institute (NCI) in the arena of complementary and alternative medicine (CAM). The website includes CAM information, research resources, the NCI Best Case Series, clinical trials, grant application information, and funding opportunities in cancer CAM.
PDQ Cancer Information Summaries: Complementary and Alternative Medicine http://cancer.gov/cancertopics/pdq/cam	Electronic resource containing summaries of complementary therapies.
PDQ Cancer Clinical Trials http://www.cancer.gov/clinicaltrials/finding/	The Physician Data Query (PDQ) holds many clinical trials in its international registry and is maintained by the NCI. Users can perform tailored searches focusing on type of cancer, trial type (treatment, supportive care, screening, prevention, genetics, diagnostic), location, status (active or closed), phase, sponsor, and drug name.
Cancer Research Portfolio http://deais.nci.nih.gov/Query/	Electronic source for searching, organising and analysing NCI-supported research by organ/cancer site and/or by broad area of scientific interest, such as biology, cancer etiology, prevention, early detection, diagnosis, prognosis, treatment, cancer control, survivorship, and outcomes research, and scientific model systems.
National Center for Complementary and Alternative Medicine (USA) http://nccam.nih.gov/	The National Center for Complementary and Alternative Medicine (NCCAM) is one of the 27 institutes and centres that make up the National Institutes of Health (NIH). Congress established NCCAM in 1998 to explore complementary and alternative healing practices in the context of rigorous science, to train complementary and alternative medicine (CAM) researchers, and to disseminate authoritative information to the public and professionals.
Office of Dietary Supplements (USA) http://ods.od.nih.gov/	The US *Dietary Supplement Health and Education Act 1994* authorised the establishment of the Office of Dietary Supplements (ODS) at the NIH to promote scientific research in the area of dietary supplements. The website covers background information about claims and labelling for dietary supplements and botanicals, tips for supplement users, how to spot health fraud, and access to US Department of Agriculture and NIH databases.
American Cancer Society http://www.cancer.org/docroot/eto/eto_5.asp?sitearea=eto	The American Cancer Society (ACS) is a nationwide community-based voluntary health organisation. With headquarters in Atlanta, Georgia, the ACS has state divisions and more than 3400 local offices. The ACS journal, *CA A Cancer Journal for Clinicians* archives numerous articles on CAM.
Consumer Labs http://www.consumerlab.com/	ConsumerLab.com, LLC (CL) provides independent test results and information to help consumers and healthcare professionals evaluate health, wellness, and nutrition products. It publishes results of its tests on its site, including listings of brands that have passed testing. Products that pass CL's testing are eligible to bear the CL Seal of Approval.
UK information service chisuk.org.uk/	Complementary health information service, UK
NCI-supported cancer research programs and cancer programs (USA)	
www.mskcc.org/patients_n_public/patient_care_services/outpatient_services_and_facilities/integrative_medicine_service/index.html	Integrative Medicine at Memorial Sloan-Kettering Cancer Center
http://www.rosenthal.hs.columbia.edu/	The Richard & Hinda Rosenthal Center for Complementary and Alternative Medicine. Columbia University

TABLE 10.5 Useful Web-Based Information Sources *continued*

Information source and URL	Description
http://www.dana-farber.org/pat/support/zakim_default.asp	Dana-Farber Cancer Institute Zakim Center for Integrated Therapies
http://cancer.duke.edu/pated/CAM.asp	Duke Comprehensive Cancer Center
http://www.hopkinsmedicine.org/cam/	The Johns Hopkins Center for Complementary and Alternative Medicine
http://www.compmed.umm.edu/	The University of Maryland Center for Integrative Medicine
http://www.mdanderson.org/departments/cimer/	The University of Texas M.D. Anderson Cancer Center Complementary/Integrative Medicine Education Resources
http://www.healthsystem.virginia.edu/internet/cancer-patients/complementary/	University of Virginia Cancer Centre Complementary Cancer Care Program
mdanderson.org/	University of Texas, complementary medicine information site

Sources: Lee 2005, Schmidt and Ernst 2004, Vickers and Cassileth 2001

For chemotherapy, for example, St John's Wort should be discontinued at least 7 days before any chemotherapy that is metabolised by the CYP3A4 enzymatic pathway or involves the P-gp transporter (see Chapter 8). Treatment may be recommenced after five times the elimination half-life of the chemotherapy agent. Making an accurate determination of appropriate washout periods is difficult owing to interpatient variability of pharmacokinetics, and the difficulty in interpreting pharmacokinetic data. As a result, a conservative estimation of the half-life is recommended.

The Micromedex database states that the drug cyclophosphamide has an elimination half-life of 3 to 12 hours (Commonwealth of Australia 2005). This means that St John's Wort should not be started until 3 days ($12 \times 5 = 60$ hours) after cessation of the cyclophosphamide. However, this has not taken into account the fact that cyclophosphamide has active metabolites that contribute to its pharmacological effect. No specific data are available in popular drug databases concerning the half-life or the metabolic pathway of the primary active metabolite, but a case study of 12 people is reported that identified 77% of the active metabolite present in serum 8 hours after administration. Assuming linear elimination kinetics, the elimination half-life of the active metabolite is extrapolated to be 17.3 hours; thus, the patient should wait for at least 86.5 hours before recommencing St John's Wort. In such cases, if the cyclophosphamide is being given at regular intervals (often every 14 or 21 days), the most practical option is to abstain throughout treatment and recommence 4 days after the final treatment cycle has ended.

The use of CMs during active chemotherapy attracts a greater risk of drug interactions and is more problematic. It is essential to gather credible information about the known and unknown benefits and risks and to provide this to patients so they can be involved in making an informed decision. If patients with a readily curable cancer experience drug-induced toxicities that jeopardise their ability to continue treatment or necessitates dose reduction, then concurrent use of antioxidants and other organ-protective treatments may be more acceptable and provide a useful option.

Difficult-to-cure cancers

When conventional treatments do not have a high cure rate, or a patient's response to treatments has been poor, then a different situation arises. The combined use of CMs with conventional treatments is more acceptable in this setting, although thoughtful judgment still applies.

Numerous CM therapies have been shown to reduce a variety of chemotherapy-related side effects and/or pose no obvious risk to patients. In addition, CMs shown to have potential to increase the efficacy of chemotherapy can be further explored (with less ethical problems) in this patient group.

For example, ovarian cancers in the advanced stages are often treated with single-agent cisplatin or carboplatin. Treatment cessation or dose reductions are most often due to toxicities and/or renal impairment. Various antioxidants have been shown to reduce chemotherapy-induced peripheral neuropathy

PRACTICE TIPS TO PROMOTE PATIENT SAFETY

1. Ask all patients about the use of CMs.
According to the literature, many patients fail to disclose use of CMs to hospital staff; however, disclosure is more likely if they are asked directly. Some patients may not understand what is meant by the term 'complementary medicine', so consider using phrases such as 'vitamins, minerals or herbal medicines' or 'natural medicines'. If a patient is also seeing a CM practitioner who is prescribing CM treatments, it may be important to contact the practitioner and start an open dialogue to promote patient safety and continuity of care.

2. Clear communication about risks and benefits, known and unknown
If a patient is using a CM that has known or suspected potential to cause adverse outcomes, an honest discussion about what is known and unknown about the risks should ensue. If the patient still wishes to continue using the CM product against professional advice, the patient should be asked to sign a form listing the potential adverse effects to acknowledge that the attending doctor or pharmacist has recommended against continued use. This should also be documented in the patient's medication history and/or discharge summary.

3. Suspend use of complementary medicines known or suspected to pose a safety risk
Pharmacokinetic data about the drugs involved in treatment will help determine appropriate washout periods.

4. If in doubt, refer to drug information centres, peer-reviewed literature or reputable resources for further information.
Evidence is accumulating about CM at a rapid rate and it would be unreasonable to expect all healthcare professionals to keep up to date with these changes. However, referring to reputable information sources when unsure about patient safety is essential for best practice.

5. Document information and recommendations in patient's chart.
Patient's CM use should be documented in the medication history and/or discharge summary as appropriate. The name, strength, brand and dose used should be recorded.

6. Consider if and when a patient can resume taking the CM.
If use of an effective CM has been withdrawn, recommencement will be required to restore the patient's response. This should be discussed when taking the medication history.

7. Recommend CMs with known safety and benefits.
If research indicates a complementary medicine has significant patient benefits and is low risk, then evidence-based practice dictates it should be considered in the patient's management. Furthermore, if a patient is experiencing beneficial outcomes from the use of a CM product in the time prior to cancer treatment and the available evidence indicates efficacy and safety, continued use should be considered and carefully monitored.

8. If an adverse event does occur, report this through the relevant channels.
Case reports provide useful clues that can guide future research to better determine factors affecting patients' safety.

(Wolf et al 2008), renal toxicity and haematological toxicity (Block et al 2007) and may play an important role in reducing additional organ damage. Some clinical studies further suggest that co-administration may improve survival outcomes. As a result, combined use of antioxidants and other CMs with chemotherapy may present patients with a good option.

Palliative care

The goal of palliative care is the achievement of the best quality of life for patients and their families. It involves the active holistic care of patients with advanced, progressive illness so they can live as actively as possible. It also involves assisting patients to die as they have lived, when the time arrives. Respecting a patient's choice during this period is of supreme importance. Providing relief from pain and other symptoms is paramount.

CM therapies are more accepted in the palliative care setting and can provide an important means of improving patients' quality of life, as the potential benefits of treatment tend to outweigh the potential risks. There is also a greater emphasis on patients' values and lifestyle habits in the delivery of quality care at the end of life, which allows more flexibility in patient care.

Besides providing physical benefits, the use of various CM therapies and medicinal treatments may provide significant psychological benefits for patients and their families if they have a strong need to feel they have tried everything possible that is available to them. The use of CM during this stage may assist them in coming to terms with the disease and subsequently help the family in the bereavement period.

Unfortunately, indiscriminate use of CM treatments during this period may also occur as patients and families search desperately for new treatments. This may have detrimental effects and place an unwanted burden on the patient physically, psychologically and financially if they comply with family wishes while suffering added discomfort to do so. In the UK, national guidelines for the use of complementary therapies in supportive palliative care provide a comprehensive overview of the key issues involved in CM provision and make recommendations for the safe and appropriate use of CM treatments in this population (Tavares 2003).

It is important to remember the ultimate decision to use or disuse CM treatments lies with the patient.

Communicating with patients

Clearly, the need for physicians to assist patients in treatment decision making is considerable and requires more than just being informed about CM. Physicians also need to have effective (and non-judgmental) communication skills to manage the discussion. They must also be prepared to provide information and advice about the benefits and likely outcomes of treatment, potential risks and complications, side effects and complementary treatment options. This information is needed to meet the traditional ethical principles of non-maleficence (do no harm) and beneficence (offer a benefit) (Verhoelf et al 2006).

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CHAPTER 11
HERBS AND NATURAL SUPPLEMENTS IN PREGNANCY

INTRODUCTION

Most women take over-the-counter medicines at some point during their pregnancy. This may occur intentionally or happen inadvertently during the early stages of pregnancy. The advice on many product labels and package inserts is to 'consult your doctor' or 'consult your healthcare provider' before using a particular medicine, yet many healthcare providers are poorly equipped to weigh up the benefits of taking, or not taking, a particular medicine during pregnancy. The risk/benefit assessment is possibly even more complex when considering the safety and efficacy of complementary medicines (CMs).

Medical and complementary medicine practitioners, pharmacists and other healthcare providers face similar challenges when advising the pregnant patient about CMs. Despite their popularity, there is very little published evidence regarding the efficacy and safety of natural medicines during pregnancy and lactation. Modern and traditional texts may warn against use, but little information is provided about the evidence upon which such a recommendation is based. Information about the potential efficacy of CMs in pregnancy is also scarce.

This chapter aims to provide readers with an introduction to the fundamental concepts and concerns surrounding the use of complementary medicines in pregnancy. Part 1 explores the use of herbs and natural supplements in pregnancy from contemporary and traditional approaches. Safety and evidence issues are discussed in Part 2. Central to this section is a discussion about the methods of establishing the safety of any medicine in pregnancy. Part 3 provides a guide to using the information in this chapter to shape clinical practice.

PART 1: USE OF HERBS AND NATURAL SUPPLEMENTS IN PREGNANCY

It is commonly known that complementary medicine (CM) is widely used throughout the world. In many countries traditional medicine continues to form the basis of primary healthcare (WHO 2002). There is a trend in developed countries, including Australia, towards an increase in the use of traditional medicine and CM (Thomas et al 2001, MacLennan et al 2002, Tindle et al 2005, Xue et al 2007). Recent literature indicates that women frequently use CM during pregnancy; however, usage estimates vary considerably owing to variations in the definition of CM used, geographical location, socioeconomic and cultural influences. For example, surveys conducted in Europe, USA and Canada indicate that the prevalence of CM usage in pregnancy ranges from 7.1% to 96% (Forster et al 2006). In Australia it is estimated that between 10% (Henry & Crowther 2000) and 91% (Forster et al 2006) of all pregnant women will use CM at some stage during their pregnancy. With regard to herbal medicines specifically, although the majority of women discontinue taking them once they know they are pregnant, some others may commence taking them on the advice of their maternity care providers (Ranzini et al 2001).

Surveys of Australian women have revealed that nutritional supplements are frequently taken before and throughout pregnancy.

During the pre-conception period, the most common supplements taken are folate (29–33%), multivitamins (11–12%) and other supplements including vitamin C, and calcium and iron (12–15%). During pregnancy, use of folate increases to 70–79% of women (particularly in the first trimester), multivitamins to 27–35%, iron to 38–52%; use of other supplements also increases, including calcium (6–24%), vitamin B_6 (1–13% predominantly in the first trimester) and zinc (1–7%). The herbal medicine most often used in pregnancy is raspberry leaf (particularly in the last trimester) (Maats & Crowther 2002, Forster et al 2006).

Despite the widespread use of CMs, pregnant women do not always disclose their use to healthcare providers. In one study only 1% of participants' medical records listed their CM use (Maats & Crowther 2002), while another study reported that 75% of women had informed their primary care provider (Tsui et al 2001). Lack of disclosure is problematic because women miss the opportunity to receive informed advice about the effectiveness and safety of the medicines they have chosen to use and prevent unsafe outcomes, while unsupervised use potentially increases the risk of drug interactions with prescribed medicines and contributes to the under-reporting of side effects and adverse outcomes.

Some pregnant women are motivated to take CMs in lieu of conventional medicines because they believe CMs to be safer (Hollyer et al 2002). Sometimes self-prescribed use is justified, such as using nutritional supplements to meet increased nutritional requirements; to treat a pregnancy-related health issue (e.g. nausea or general pregnancy preparation); or to treat non-pregnancy-specific problems (e.g. the common cold) (Henry & Crowther 2000, Maats & Crowther 2002, Nordeng & Havnen 2004).

Pregnant women appear to use a variety of information sources to aid their selection of CMs, including healthcare practitioners (Tsui et al 2001, Forster et al 2006), friends, family members (Tsui et al 2001, Hollyer et al 2002, Maats & Crowther 2002, Nordeng & Havnen 2004) and media sources (e.g. magazines and the internet) (Tsui et al 2001).

NUTRITIONAL MEDICINE

Pregnant women may choose to use nutritional medicines as symptomatic treatment to improve their own general health and to optimise the healthy development of the growing child and its safe delivery.

Most clinicians will be aware of the changes in nutritional requirements that occur in pregnancy and the need for women to increase their dietary intake of certain nutrients such as iron, calcium, folate and others. Nutritional supplements are sometimes used to help women achieve these higher intake levels and to correct preexisting deficiencies. The National Health and Medical Research Council's nutritional guidelines for the adequate intake of vitamins and minerals (NHMRC 2006) are a guide for nutritional requirements during pregnancy. However, these guidelines are only estimates based on extrapolated data from other populations and models and do not take into account the individual's specific needs. In practice, a detailed diet and lifestyle history and sometimes additional pathology testing are necessary so that clinicians can make more appropriate individual recommendations.

Besides enabling women to meet their basic nutritional needs, nutritional supplements are also used in larger doses to act as pharmacological agents to ameliorate symptoms and address specific health complaints. For example, calcium and magnesium supplements have been used to reduce the severity of leg cramps, pyridoxine to alleviate nausea, and folate to reduce the incidence of neural tube defects. Table 11.1 (pp 151–6) lists common nutritional supplements and their use in pregnancy.

Long-term impact of maternal nutrition

The 'developmental origins of disease' hypothesis suggests that the benefits of a nutritional intervention may extend much further than the more immediate outcomes. Environmental factors during development, such as maternal nutrition, have been shown to influence the expression of our phenotype. The most sensitive time for this influence has been shown to be in utero. Fetal nutrition can alter the body's structure, function and metabolism, subsequently affecting the risk of developing diseases later in life (Barker 2004). Longitudinal studies from around the world have found that low birth weight (in relation to gestational age) is associated with an increased risk of coronary heart disease, stroke, hypertension and type 2 diabetes in adulthood (Barker 2007). Furthermore, maternal vitamin D status during pregnancy appears to influence the bone-mineral density of offspring even in late childhood (Javaid et al 2006). Similarly, there is some evidence to suggest that calcium supplementation during pregnancy can reduce

TABLE 11.1 Nutrients During Pregnancy

Nutrient	Therapeutic function/justification	Dosage recommendations and issues
Vitamin A	• Required for gene expression and cellular differentiation in organogenesis and embryonic development of the spinal cord and vertebrae, limbs, eyes and ears, and heart (Morriss-Kay & Sokolova 1996). • Poor maternal status will result in risk of infant deficiency (Ortega et al 1997) associated with poor immune function and increased risk of infection morbidity and mortality in infants and children (Grubesic 2004, Huiming et al 2005). • Maternal deficiency increases the risk of mortality (West et al 1999), premature rupture of membranes (Westney et al 1994), preterm delivery (Radhika et al 2002), reduced haemoglobin levels and anaemia (Suharno et al 1993, Bondevik et al 2000), night blindness (Livingstone et al 2003) and immune suppression (Cox et al 2006).	• Excessive supplementation shown to be associated with adverse pregnancy outcomes, particularly in the first trimester. • No association between moderate intake (< 10,000 IU) and fetal malformations (Martinez-Frias & Salvador 1990, Werler et al 1990, Botto et al 1996, Mills et al 1997, Shaw et al 1997, Mastroiacovo et al 1999, Johansen et al 2008). • Supplement labels must carry the warning, 'When taken in excess of 3000 μg retinol equivalents (10,000 IU), vitamin A may cause birth defects'.
Vitamin B_6 (pyridoxine)	• Beneficial in the treatment of nausea in pregnancy (Jewell & Young 2003, Sripramote & Lekhyananda 2003, Jamigorn & Phupong 2007). • Poor vitamin B_6 status may decrease the possibility of conception (Ronnenberg et al 2007) and increase the risk of early pregnancy loss (Wouters et al 1993, Goddijn-Wessel et al 1996, Ronnenberg et al 2007).	• RDI during pregnancy is increased slightly to 1.9 mg, and upper recommended level is 50 mg with no evidence of teratogenicity. • High-dose supplementation (mean 132 mg/day) for 9 weeks during the first trimester appears to be safe, with no associated increase in risk for major malformations (Shrim et al 2006). Doses used in studies for nausea are 30–75 mg/day.
Vitamin B_9 (folic acid)	• Deficiency can lead to homocysteine accumulation, which may be associated with abnormalities of the placental vasculature and increased risk of miscarriage and preeclampsia (Dodds et al 2008, Napolitano et al 2008, Makedos et al 2007) and is associated with a two-fold increased risk of adult schizophrenia (Brown et al 2007). • Intake of folic acid pre-conceptually and during the first 4–6 weeks of pregnancy reduces the risk of neural tube defects (NTDs) by more than 50% (Czeizel & Dudas 1992, Berry et al 1999) and may also decrease the risk of other congenital malformations, including urinary tract and cardiovascular defects, limb deficiencies and hypertrophic pyloric stenosis (Czeizel 1998). Individuals with polymorphisms in folate metabolism (methylenetetrahydrofolate reductase [MTHFR] gene) may be at greater risk of deficiency and subsequent adverse effects (Coppede et al 2007, Biselli et al 2008, Boyles et al 2008, Candito et al 2008, Steer et al 2008). In this instance, 5-methyl-tetrahydrofolate preparations are more advisable.	• Supplementation with folate has been linked to increased risk of multiple pregnancies (Czeizel 1998, Czeizel & Vargha 2004) but this has been disputed by others (Li et al 2003). • RDI in pregnancy is 600 mcg/day (200 mcg above RDI in non-pregnancy state). Upper limit recommended in pregnancy 1000 mcg — due to the possibility of masking a vitamin B_{12} deficiency.
Vitamin B_{12} (cyanocobalamin)	• Inadequate cobalamin status in pregnancy has been associated with several adverse outcomes such as preterm birth (Ronnenberg et al 2002), intrauterine growth-retardation (Muthayya et al 2006), increased risk of NTDs (Kirke et al 1993, Wright 1995, Steen et al 1998, Suarez et al 2003, Groenen et al 2004, Gaber et al 2007) and increased risk of miscarriage (Hubner et al 2008). • Vitamin B_{12} is also required for homocysteine metabolism; increased levels have been associated with numerous conditions including preeclampsia (Napolitano et al 2008) and recurrent pregnancy loss (Hubner et al 2008). Inadequate maternal status may result in an infant with poor stores, and this may be further exacerbated by low stores in breast milk (Allen 1994).	• The RDI is slightly increased to 2.6 mcg/day in pregnancy. There is no upper level of intake as there is no evidence of adverse effects. • Deficiency (indicated by macrocytic changes) may be masked by high-dose folic acid supplementation.

Continued

TABLE 11.1 Nutrients During Pregnancy *continued*

Nutrient	Therapeutic function/justification	Dosage recommendations and issues
Vitamin C	• It has been suggested that vitamin C deficiency plays a role in several adverse pregnancy outcomes, such as preeclampsia, intrauterine growth restriction and pre-labour rupture of fetal membranes (PROM). A recent Cochrane Review, however, reported no difference for the risk of stillbirth, miscarriage, birth weight, placental abruption or intrauterine growth restriction between women supplemented with vitamin C (alone or combined with other supplements) and those given a placebo (Rumbold & Crowther 2005a, Rumbold et al 2005). • Required for healthy immune function and significantly reduces the risk of urinary tract infections during pregnancy (Ochoa-Brust et al 2007).	• The recommended intake of vitamin is slightly increased in pregnancy to 60 mg/day. • Early reports of high-dose maternal supplementation causing 'conditioned or rebound scurvy' in infants (Cochrane 1965, Rhead & Schrauzer 1971) have not been replicated in subsequent studies (Diplock et al 1998).
Vitamin D	• High prevalence of vitamin D deficiency in pregnancy and lactation has been reported (Hollis & Wagner 2004, Sachan et al 2005, Ainy et al 2006, Judkins & Eagleton 2006, van der Meer et al 2006). • Maternal vitamin D status affects the infant's vitamin D status (Hollis & Wagner 2004), intrauterine growth of long bones (Morley et al 2006), poor infant skeletal growth and mineralisation (Zeghoud et al 1997) and, in severe maternal deficiency, an increased risk of rickets in the infant (Specker 1994). Glucose intolerance (Maghbooli et al 2008), bone health and risk of osteoporotic fracture later in life may also be influenced (Javaid et al 2006). • Vitamin D is important for normal brain development (Eyles et al 2003, Cui et al 2007) with fetal deficiency leading to alterations in brain structure and function (Feron et al 2005, Almeras et al 2007). • Supplementation may protect against multiple sclerosis (Munger et al 2004, 2006) and reduce the risk of later preeclampsia in the infant (Hypponen et al 2007). • Conversely, maternal concentrations of > 75 nmol/L of 25(OH)-vitamin D in pregnancy may increase the risk of eczema in infants and asthma in children, but has not negatively influenced the child's intelligence, psychological health or cardiovascular system (Gale et al 2008).	• The amount of vitamin D required during pregnancy and lactation to avoid deficiency may be higher than the recommended amount (RDI 5.0 mcg) (Vieth et al 2001a, Hollis 2005, 2007). The recommended upper limit is 80 mcg (NHMRC 2006). Vieth et al (2001a), however, found no adverse effects even at doses of 100 mcg (4000 IU) per day. Toxicity is rare but may occur with excessive supplementation (Koutkia et al 2001). • Breast milk is a poor source of vitamin D with infants requiring an exogenous source within a few months (Sills et al 1994, Daaboul et al 1997, Challa et al 2005, Hatun et al 2005).
Vitamin E	• Antioxidant activity is valuable in protecting the embryo (in vitro) and fetus from damage due to oxidative stress (Wang et al 2002, Jishage et al 2001, Cederberg et al 2001). Although oxidative stress plays an important role in the pathogenesis of preeclampsia (Gupta et al 2005), there is little evidence for the role of vitamin E in its prevention (Rumbold & Crowther 2005b, Polyzos et al 2007). Some evidence suggests that in women with poor antioxidant status it was beneficial (Rumiris et al 2006). • Low maternal levels contribute to increased risk of wheezing and asthma in childhood (Devereux et al 2006), and supplementation was useful in reducing pregnancy-related leg cramps (Shahraki 2006) and in increasing birth weight for gestation (Valsecchi et al 1999, Scholl et al 2006).	• The recommended intake for vitamin E (7 mg) is not increased for pregnancy. High-dose supplementation of vitamin E (400–1200 IU) appears to be safe and does not increase risk for major malformations, preterm deliveries, miscarriages and stillbirths (Boskovic et al 2005). The recommended upper limit in pregnancy is 300 mg/day (NHMRC 2006).

TABLE 11.1 Nutrients During Pregnancy *continued*

Nutrient	Therapeutic function/justification	Dosage recommendations and issues
Vitamin K	• Poor maternal vitamin K levels can lead to relative deficiency in newborn infants (Shearer 1992). Low intake combined with the reduced gastrointestinal bacterial synthesis puts infants at risk of Vitamin K deficiency bleeding (VKDB) owing to the lack of activity of vitamin-K-dependent clotting factors (II, VII, IX and X) (von Kries et al 1993). This is compounded in breast-fed infants, as breast milk contains lower levels than formula, although this may be increased with maternal supplementation during lactation (Greer et al 1997).	• The recommended intake of vitamin K during pregnancy and lactation is the same as for a non-pregnant woman (60 mcg/day). To prevent infant health risks, prophylactic treatment of one intramuscular injection of 1 mg (0.1 mL) or three 2 mg (0.2 mL) oral doses at birth, 3–5 days of age and at 4 weeks are recommended (NHMRC 2000).
Calcium	• The newborn infant skeleton holds approximately 20–30 g calcium (Prentice 2003), 80% of which is acquired during the third trimester when the fetal skeleton is rapidly mineralising (Trotter & Hixon 1974). This increased demand for calcium during pregnancy is met by alterations to maternal calcium metabolism, particularly a two-fold increase in calcium absorption mediated by increases in 1,25-dihydroxyvitamin D and other mechanisms (Kovacs & Kronenberg 1997, Prentice 2003). • A possible inverse relationship between calcium intake during pregnancy and risk of hypertension and preeclampsia has been suggested from epidemiological and clinical studies (Villar et al 1983, Villar et al 1987, Repke & Villar 1991). Supplementation (1.0–2.0 g/day) is recommended to reduce the risk of preeclampsia and gestational hypertension (Hofmeyr et al 2006, Hofmeyr et al 2007); it may also reduce the blood pressure of the offspring (Belizan et al 1997, Hatton et al 2003). • Calcium supplementation during pregnancy has been shown to reduce maternal blood lead concentrations by an average of 11% by inhibiting the mobilisation of lead from bone and inhibiting intestinal absorption (Téllez-Rojo et al 2006). Supplementation (1200 mg) during lactation also reduces the risk of infant lead exposure by decreasing the concentration in breast milk by 5–10% (Ettinger et al 2006).	• Although pregnancy is a time of high calcium requirement, there is no increase in the RDI for pregnancy (1000 mg). If supplementation is required, it appears to be safe to use (Hofmeyr et al 2006).
Chromium	• Deficiency is believed to have an effect on glucose intolerance (Jovanovic-Peterson & Peterson 1996, Jovanovic & Peterson 1999). Chromium may protect against maternal insulin resistance and gestational diabetes (Morris et al 2000); however, studies are contradictory (Aharoni et al 1992, Gunton et al 2001, Woods et al 2008).	• Recommended daily intake during pregnancy is slightly increased to 30 mcg/day. • Supplementation in gestational diabetes is likely to be safe (Jovanovic & Peterson 1999).

Continued

TABLE 11.1 Nutrients During Pregnancy *continued*

Nutrient	Therapeutic function/justification	Dosage recommendations and issues
Iodine	• Iodine deficiency occurs in both developing and developed countries (Becker et al 2006). Deficiency during pregnancy (defined as urinary iodine concentrations < 150 mcg/L) has been found even in areas considered to have generally adequate intake. In a study conducted in Rome, where a salt iodination program has been introduced, only 4% of non-pregnant women were found to be iodine deficient (< 100–199 mcg/L) compared to 92% of pregnant women, suggesting that it may be necessary to monitor pregnant women even in regions where iodine deficiency is not common (Marchioni et al 2008). It enables the manufacture of maternal thyroid hormones, is protective against cretinism (Delange 2000), is vital for the development of the fetal brain, protects against neurological damage (Perez-Lopez 2007), and is also supplied to the breastfed infant via breast milk (Berbel et al 2007). • Maternal hypothyroidism during early pregnancy is associated with other adverse outcomes including premature birth, preeclampsia, breech delivery and increased fetal mortality (Haddow et al 1999, Pop et al 2004, Casey et al 2005). High-risk women (personal or family history of thyroid disorders or a personal history of other autoimmune diseases) have more than a six-fold increased risk of hypothyroidism during early pregnancy (Vaidya et al 2007).	• Mild iodine deficiency (median UIE < 100 mcg/L) has been found in several areas in Australia, including New South Wales and Victoria (Li et al 2006). • To prevent iodine deficiency disorders, the World Health Organization (WHO), United Nations Children's Fund and International Council for the Control of Iodine Deficiency Disorders established that for a given population median urinary iodine concentrations (UIC) must be 150–249 mcg/L in clinically healthy pregnant women (Marchioni et al 2008). • Iodine requirement increases during pregnancy and recommended intakes are 250–300 mcg/day (Delange 2007). • To monitor iodine status, WHO suggest that a median urinary iodine concentration > 250 mcg/L and < 500 mcg/L indicates adequate iodine intake in pregnancy (Zimmermann 2007).
Iron	• Iron requirements increase significantly in pregnancy to support expansion of maternal red blood cell mass and fetal growth (Bothwell 2000). • Accurate assessment of iron status during pregnancy is more challenging owing to the physiological changes occurring at this time (Milman et al 1991). Haemodilution affects iron parameters such as haemoglobin concentration, haematocrit, serum iron, ferritin and total-iron binding capacity. Serum ferritin is regarded as the most reliable indicator of iron stores (Byg et al 2000), while haemoglobin levels are used as an inexpensive marker to diagnose anaemia (Reveiz et al 2007). The evaluation of iron status and of the risk of anaemia developing during pregnancy may be more accurate when done early in pregnancy before the maternal plasma volume expands (Scholl 2005). Demands are partly met by a progressive increase in iron absorption as the pregnancy advances (Bothwell 2000); however, depending on initial iron reserves, this may not be sufficient to prevent deficiency (Casanueva et al 2003). The risk of iron deficiency increases with parity (Looker et al 1997). Maternal iron stores at conception appear to be a strong predictor of the risk of anaemia in later pregnancy (Bothwell 2000, Casanueva et al 2003). WHO estimates indicate that iron deficiency anaemia affects 22% of women during pregnancy in industrialised countries and 52% in non-industrialised countries (WHO 1992). • Supplementation raised haemoglobin levels by 7.5 g/dL and reduced the risk of iron deficiency and iron-deficiency anaemia at term (Pena-Rosas & Viteri 2006).	• The RDI of iron during pregnancy is increased to 27 mg/day. Upper limit is 45 mg based on the risk of side effects and potential systemic toxicity. A daily supplement of 40 mg ferrous iron from 18 weeks' gestation appears adequate to prevent iron deficiency in 90% of women (Milman et al 2005). However, individual assessment of iron status in early pregnancy may be useful to tailor the appropriate prophylaxis to prevent iron deficiency and iron deficiency anaemia: ferritin ≤ 30 mcg/L — 80–100 mg ferrous iron/day; ferritin 31–70 mcg/L — 40 mg ferrous iron/day; those with ferritin > 70 mcg/L do not require supplementation (Milman et al 2006). • High-dose supplementation may reduce the absorption of zinc (Hambidge et al 1987, O'Brien et al 2000) and other divalent cations (copper, chromium, molybdenum, manganese, magnesium) (Rossander-Hulten et al 1991). • Side effects of high-dose supplementation typically include gastrointestinal disturbances, most commonly constipation and nausea (Melamed et al 2007).

TABLE 11.1 Nutrients During Pregnancy *continued*

Nutrient	Therapeutic function/justification	Dosage recommendations and issues
	• Numerous studies have showed an association between adverse outcomes and iron deficiency anaemia, including increased risk of maternal mortality, infection, low birth weight and premature delivery. Fetal and infant iron deficiency may adversely impact on brain development, function and neurocognition (Grantham-McGregor & Ani 2001). Poor maternal iron status may contribute to reduced fetal stores (Preziosi et al 1997, de Pee et al 2002, Emamghorashi & Heidari 2004). However, in a recent cross-sectional study pregnant women with iron deficiency or mild anaemia were not found to produce offspring with significantly altered iron levels (Paiva Ade et al 2007). Similarly, iron supplementation during the second half of pregnancy was not found to influence the iron status of the children at 6 months or 4 years of age (Zhou et al 2007). On a cautionary note, excessive iron supplementation resulting in high haemoglobin and increased iron stores may be associated with increased adverse pregnancy outcomes (Scholl 2005), including low birth weight and premature delivery (Casanueva & Viteri 2003).	
Magnesium	• Magnesium is involved as a co-factor in more than 300 enzyme pathways (Wacker & Parisi 1968) and acts as a neuromuscular relaxant. The infant has stored approximately 750 mg at birth (Prentice 2003). • Positive trials highlight the benefits of magnesium supplementation for leg cramps (Dahle et al 1995) and possibly for preeclampsia, although evidence is inconsistent for this last indication (Dawson et al 2000, Kisters et al 2000, Adam et al 2001, Duley et al 2003, Ahmed 2004, Shamsuddin et al 2005, Omu et al 2008, Seydoux et al 1992, Handwerker et al 1995, Sanders et al 1999, Makrides & Crowther 2001).	• The RDI for magnesium during pregnancy is increased slightly to 350 mg (age 19–30 years) and 360 mg (31–50 years). The upper level of intake from non-food sources is 350 mg/day.
Zinc	• Zinc deficiency has been associated with adverse outcomes in pregnancy. Numerous animal models demonstrate an association between zinc deficiency and increased developmental abnormalities and fetal losses. Deficiency has also been associated with reduced interuterine growth, preterm delivery, labour and delivery complications, poor immunological development (Caulfield et al 1998) and congenital malformations (Hambidge et al 1977). In humans, acrodermatitis enteropathica, a genetic disease that produces severe zinc deficiency, has been found to increase fetal losses and malformations, most probably owing to the key role it plays in protein synthesis and cellular growth (King 2000). • The usefulness of zinc supplementation during pregnancy is unclear. Supplementation has been shown to reduce preterm birth (Mahomed et al 2007), assist the accumulation of lean tissue in the infant during the first year of growth (Iannotti et al 2008) and reduce the risk of delivering via caesarean section (Mahomed et al 2007). • While women with preeclampsia have significantly lower zinc and superoxide dismutase (SOD) levels compared to healthy pregnant women (Ilhan et al 2002), zinc supplementation had no significant effect in pregnancy hypertension or preeclampsia (Mahomed et al 2007); and no significant differences were seen for several other maternal or infant outcomes, including pre-labour rupture of membranes, antepartum haemorrhage, post-term birth, prolonged labour, retention of placenta, meconium in liquor, smell or taste dysfunction, maternal infections, gestational age at birth or birth weight (Mahomed et al 2007).	• During pregnancy, RDI is increased to 11 mg/day, and the recommended upper level of intake is the same as for adults, at 40 mg/day. Vegans/vegetarians may need an additional 50%. • The teratogenic effects of alcohol may be exacerbated by a concurrent zinc deficiency (Keppen et al 1985).

Continued

TABLE 11.1 Nutrients During Pregnancy *continued*

Nutrient	Therapeutic function/justification	Dosage recommendations and issues
Omega-3 DHA/EPA)	• High fetal demands for omega-3 fatty acids result in the progressive decrease of maternal stores throughout pregnancy (Al et al 1995, Bonham et al 2008). • Omega 3 is important for optimal fetal and infant neurodevelopment and may be associated with benefits for other pregnancy and infant health outcomes, including growth and development of the fetal and infant brain (Horrocks & Yeo 1999), improvements to children's eye–hand coordination (Dunstan et al 2008) and higher infant cognitive function (Oken et al 2005, Hibbeln et al 2007). • Lower maternal intake was associated with: increased risk of infants with poorer outcomes for prosocial behaviour, fine motor ability, communication, and social development scores (Hibbeln et al 2007); increased risk of infant asthma (Olsen et al 2008), increased risk of postnatal depression (Levant et al 2006, 2008) and increased depressive symptoms in postpartum women (Hibbeln 2002). However, more recent studies have found no associations (Browne et al 2006, Sontrop et al 2008, Rees et al 2008, Freeman et al 2008) or mixed outcomes (Su et al 2008). • Lower dietary intake of fish (Oken et al 2007), and biochemical markers of omega-3 fatty acid intake (Velzing-Aarts et al 1999, Qiu et al 2006, Mehendale et al 2008) have been reported in women who develop preeclampsia. Intervention studies with fish oil supplementation, however, generally have not found a protective effect. In a recent Cochrane Review there was no significant difference in risk of gestational hypertension (five trials) or preeclampsia (four trials) between those taking the fish oil (133 mg/day to 3 g/day) and control groups (Makrides et al 2006).	• Fish oil supplementation during pregnancy appears to be safe. Mild side effects such as belching and unpleasant taste are reported (Makrides et al 2006, Freeman & Sinha 2007). • Recommendations for dietary intake of EPA/DHA (adequate intake) for pregnancy is 115 mg/day. An upper level of intake of 3 g is recommended for adults (no pregnancy specifications). • Maternal dietary DHA intake of at least 200 mg/day is associated with positive infant neurodevelopmental outcomes (Cetin & Koletzko 2008).
Probiotics	• Prenatal and postnatal supplementation with probiotics may play a role in immune regulation and the prevention of allergies developing in the infant. Numerous positive studies in the prevention of allergies, including eczema, in the child have involved the following strains: *Lactobacillus reuteri* (ATCC 55730) (Abrahamsson et al 2007) *L. rhamnosus* GG (ATCC 53103) (Kalliomaki et al 2001, Rautava et al 2002, Kalliomaki et al 2003) *L. rhamnosus* GG (ATCC 53103); *L. rhamnosus* LC705 (DSM 7061); *Bifidobacterium breve* Bb99 (DSM 13692); and *Propionibacterium freudenreichii* ssp. *shermanii* JS (DSM 7076) (Kukkonen et al 2007) *L. rhamnosus* GG and *B. lactis* Bb12 (Huurre et al 2008) • Prophylactic enteral supplementation reduces the occurrence of necrotising enterocolitis and death in premature infants born weighing less than 1500 g (Alfaleh & Bassler 2008); this may be owing to normalisation of gut flora and stimulation of natural host defences (Hammerman & Kaplan 2006). • Vaginal application reduces the risk of vaginal infections in pregnancy (Othman et al 2007).	• Based on review of literature, prescription appears to be safe for internal and vaginal application.
Choline	• Choline status in pregnancy influences the development of the memory centre (hippocampus) in the fetal brain, and may have a life-long impact on memory (Zeisel 2004).	• The RDI is slightly increased at 440 mg/day, with an upper level of 3000 mg/day.

the offspring's blood pressure during childhood (Hatton et al 2003).

HERBAL MEDICINE

Herbal medicines are used in pregnancy as pharmacological agents. They are used as foods, such as ginger, in extract form (liquid and solid dose forms) and also as teas. In many developing countries, herbal medicines have been used as the dominant form of medicine and continue to play a major role in healthcare, reproductive health and midwifery (WHO 2002).

A traditional approach

Although conception is a problem for some women, a more common problem throughout the ages was contraception. Ethnobotanical studies conducted in many parts of the world reveal that herbal medicines have been used widely for generations to prevent conception and induce miscarriage, and in some parts of the world their use continues despite the availability of pharmaceutical contraceptive pills and devices. Besides this, herbal medicines have been used to enhance fertility, regulate menstruation, facilitate childbirth, help with the expulsion of the placenta and promote lactation.

In many cultures, herbal healers have special reverence for herbs that are thought to have abortifacient or emmenagogue properties. These concepts are foreign in Western medicine and deserve some discussion.

Abortifacients

Since ancient Egyptian times, plants have been used as a source of both contraceptives and early-term abortifacients (Riddle 1991) and in some parts of the world this practice still exists. The abortifacient effects of herbs are attributed to their inherent toxicity or ability to induce uterine contractions (Noumi & Tchakonang 2001). It is also suspected that abortifacient activity may be immune-mediated, hormonal or due to non-specific actions, such as the ability to reduce uterine blood flow. Examples of Western herbs with abortifacient potential due to suspected toxicity include wormwood (*Artemsia absinthium*), pennyroyal (*Mentha pulgeum*), poke root (*Phytolacca decandra*), pau d'arco (*Tabebuia avellanedae*), rue (*Ruta graveolens*) and tansy (*Tanacetum vulgare*) (Mills & Bone 2005).

Emmenagogues

The term 'emmenagogue' is used to describe a herb that will stimulate menstrual flow. Traditionally, such herbs have been indicated for delayed menstruation and have developed a reputation of being contraindicated in pregnancy for fear they may induce miscarriage. Herbalists consider emmenagogues to exert oxytocic-like effects that cause uterine contractions; however, this mechanism is unlikely to explain how they promote menses in a non-pregnant woman. Changes to lymph or blood flow and hormonal effects are more likely mechanisms. Examples of herbs thought to act as emmenagogues found on many traditional lists include aloe (*Aloe vera*), juniper (*Juniperus communis*), pennyroyal (*Mentha pulgeum*), goldenseal (*Hydrastis canadensis*), black cohosh (*Cimicifuga racemosa*), blue cohosh (*Caulophyllum thalictroides*), dong quai (*Angelica polymorpha*), rue (*Ruta graveolens*), tansy (*Tancetum vulgare*) and thuja (*Thuja occidentalis*). Some herbs considered to be emmenagogues are also regarded as potential abortifacients if used in sufficient quantities (e.g. oxytocin agonists); however, not all abortifacients may act as emmenagogues (e.g. potentially toxic herbs with no hormonal or uterine effects).

Historical perspectives

Medicinal plants have been used in Mexico since pre-Hispanic times. Nearly 10 million indigenous people speaking nearly 85 different languages inhabit the region, and many still depend for primary therapy upon plants from the diverse flora (almost 5,000 medicinal plants) (Andrade-Cetto 2009). An ethnobotanical study of the medicinal plants from Tlanchinol, Hidalgo, Mexico, identified several plants that are used as abortifacients (Andrade-Cetto 2009): *Galium mexicanum* var *mexicanum, Ruta chalepensis*, *Zaluzania triloba* and *Tanacetum parthenium*. The herb *Cinnamomum veru* is generally considered useful to induce childbirth and *Pedilanthus tithymaloides* to reduce ovarian pain.

The Criollo people of Argentina use a vast plant pharmacopoeia. To date, 189 species with 754 different medicinal applications have been recorded (Martinez 2008). The absence of a normal menstrual cycle and amenorrhoea are matters of concern among the Criollo and are treated with emmenagogue plants, the most common being *Anemia tomentosa*, *Tripodanthus flagellaris*, *Lippia turbinata* and *Trixis divaricata*. Contraceptive herbs used in the region include *Zea mays*, *Anemia tomentose*, and abortifacient herbs include *Artemisia absinthium*, *Cheilantes buchtienii*, *Chenopodium aff. hircinum*, *Cuphea glutinosa*, *Ligaria cuneifolia, Lippia turbinate* and *Pinus* spp (Martinez 2008).

Rama midwives in eastern Nicaragua currently use a diverse group of plants in the practice of midwifery: 162 species from 125 genera and 62 families (Senes et al 2008). This extensive ethnopharmacopoeia is employed to treat the many health issues of pregnancy, parturition, postpartum care, neonatal care and primary healthcare of women and children. The 22 most popular midwifery species are medicinals that are widely used by practitioners other than midwives, not only in eastern Nicaragua but elsewhere. Very few herbal species are used as contraceptives in this region, whereas abortifacients are well known and mostly made with bitter-tasting plants (the bitter taste is probably due to alkaloids and other bitter-tasting compounds). The most widely used abortifacients are decoctions made from the leaves and seeds of soursap and the roots of guinea hen. Others are decoctions made with the leaves and/or flowers of barsley, broom weed, trompet, sorosi and wild rice, and from the root of ginja.

Interestingly, midwives in other parts of the world use many Rama midwifery species for the same purpose: for example, sorosi and lime are both widely regarded as important in midwifery. Sorosi is one of the most widely used medicinals in eastern Nicaragua, where it is used as an abortifacient, with similar use in Africa, Australia, Brazil, India, Malaysia, the Philippines and the West Indies (Senes et al 2008). Lime is a domesticated crop used by the Rama and other indigenous groups of eastern Nicaragua as an abortifacient and to accelerate labour. It is also used to induce abortion by tribal people in India, Honduran midwives and the Tikunas of northwestern Amazonia.

In Europe, herbal medicine has a rich history and continues to be popular today. As in other parts of the world, plants were used for reproductive health, to prevent conception and induce abortion, with women and midwives as the main keepers of herbal knowledge. Savin (*Juniperus sabina*) was one abortifacient herb of choice and pennyroyal, sage, thyme and rosemary were considered powerful emmenagogues (Belew 1999). Unlike some other parts of the world, information exchange down the generations was interrupted during the 18th and 19th centuries because there was a major shift in the management of the birthing process (Schiebinger 2008). During this period, female practitioners with knowledge of herbal lore lost ground to obstetricians (men trained primarily as surgeons), and plant-based treatments were gradually replaced with surgical procedures (Schiebinger 2008). As a result, much knowledge about the use of herbal medicines in fertility and reproduction in Europe was lost.

The North American Indians used herbal medicines extensively throughout the reproductive life cycle and had many remedies for improving fertility, preventing miscarriage, treating symptoms during pregnancy and facilitating the birthing process. A large number of these treatments became known to European settlers in North America through careful study, observation and subsequent clinical use. If repeated use indicated the treatments were effective, the herbs were recorded and prescribed by the Eclectic physicians, who flourished from the mid-1800s to around 1920 in the United States (Belew 1999). Many of the herbal medicines used by the North American Indians and described by the Eclectic physicians are still in use today as part of the Western herbalists' and traditional midwives' cache of treatments.

The Eclectics considered black cohosh a 'remedy par excellence to stimulate normal functional activity of the uterus and ovaries' throughout the reproductive life cycle (Belew 1999). They reported that when used regularly at the end of pregnancy 'it will render labor easier and quicker, and give a better getting up'. Black haw was highly regarded by the Eclectic physicians, who used it both before and during pregnancy to prevent miscarriage, prepare for labour and relieve false labour pains and after-pains. The Eclectic physicians preferred to use cottonroot (*Gossypium*) as an oxytocin agonist rather than the newly available sublingual oxytocin preparation, because the herb was considered to have a gentler action and produce more predictable results. Squaw vine (*Mitchella repens*) was well considered when enhanced fertility was called for. It was extensively used to promote menstruation and alleviate physical discomfort in the latter months of pregnancy, and was thought to be a good preparative to labour, rendering the birth easier.

Contemporary use by Western herbalists

In Western herbal practice today, much knowledge about herbal safety and efficacy in pregnancy is drawn from North American and European traditions, and traditional applications are largely used as a basis for prescriptions. Herbal medicines may be prescribed to

regulate menstruation before conception, and to alleviate morning sickness and other symptoms related to pregnancy. A growing number of gynaecologists and obstetricians are working with herbalists to enhance patients' chances of conception and reducing miscarriage, sometimes in combination with IVF procedures.

Requests for abortifacient herbs in Western countries are virtually unheard of; however, some women still seek herbalists to provide '*partus* (birth) *preparatus* (prepare)' mixtures to prepare for childbirth and facilitate delivery. Traditionally, the Eclectic physicians called these preparations 'mother's cordial'. They tend to be recommended in very low doses, starting at 36 weeks' gestation, with the dose increasing each week until delivery. Herbs that have been used in *partus preparatus* preparations include: *Mitchella repens* (squaw vine), *Viburnum prunifolium* (black haw), *Rubus idaeus* (raspberry), *Chamaelirium luteum* (false unicorn), *Caulophyllum thalictroides* (blue cohosh) and *Cimicifuga racemosa* (black cohosh).

Today, Western herbalists are also asked for treatment to address pre- and postnatal depression, and to alleviate symptoms of dyspepsia, nausea and lower back pain, and sometimes for topical applications to reduce perineal discomfort and stretch marks associated with pregnancy. In addition, herbalists may be providing support for conditions unrelated to pregnancy, such as urinary tract or upper respiratory tract infections.

Unlike medical practitioners, Western herbalists are less concerned about teratogenicity than inducing miscarriage. To minimise the risk of harming the mother or fetus, several general guidelines are followed. Most importantly, traditional sources dictate that if known toxic herbs are avoided, then toxic side effects are unlikely to occur. In addition, other classes of herbs avoided during pregnancy include the following (Hess et al 2007):

- emmenagogues and abortifacients (discussed below)
- large quantities of herbs containing a high volatile oil content, especially during the first trimester (It is suspected that volatile oils contain constituents that could induce uterine contractions. Many kitchen spices contain volatile oils: they are not believed to be a problem when used in dietary amounts but could pose problems when used in concentrated preparations [e.g. rosemary, peppermint, thyme, sage]. This contraindication is likely to be derived from European tradition, as there is scant scientific evidence to support this concern.)
- stimulant laxative herbs containing anthraquinones (These herbal medicines stimulate peristalsis and can induce loss of water and electrolytes, intestinal cramps, loose bowels and dependency with chronic use. It is believed these harsh irritant effects may exert a reflex stimulating effect on the uterus, causing uterine contractions. This is a traditional understanding, as there is no scientific evidence to support this concern at present. Stimulant laxative herbs include buckthorn, cascara [*Rhamnus* sp.], rhubarb, castor, senna and aloe. Aloe gel is not a problem, as it contains a part of the plant that does not contain significant levels of anthraquinones.)
- herbs with hormonal actions such as *Trifollium pratense* (red clover) and *Vitex agnus-castus* (chaste tree), which may adversely influence fetal development
- thujone-containing herbs such as *Achillea millefolium* (yarrow), *Thuja occidentalis* (thuja) or *Artemisia absinthium* (wormwood) due to their inherent toxicity concerns.

This approach is based on traditional evidence and theoretical concerns, usually without any scientific evidence to confirm lack of safety. As such, a herbalist's approach to these herbs may be overly cautious and not borne out if scientific testing takes place in the future. For example, senna is traditionally avoided during pregnancy as it is an anthraquinone-containing herb, but it is widely recommended as a safe and effective short-term stimulant laxative for constipation by medical practitioners (Tytgat et al 2003). Some herbalists also recommend against the use of several aromatherapy oils during the first trimester, but there is no scientific evidence to suggest external use of such oils poses any serious danger.

PART 2: SAFETY IN PREGNANCY

All medicines have the potential to affect maternal health, and to cross the placenta and affect fetal development. The most serious risk associated with medicine use in pregnancy is the possibility of teratogenesis, which can manifest as a structural abnormality, dysfunctional growth in utero and/or long-term functional defects. Other risks include miscarriage and neonatal withdrawal.

Birth defects occur naturally in 2–4% of all newborns and in the vast majority of cases the

cause is unknown. Medication use is not considered a major contributor to the incidence of birth defects, as less than 1% of cases can be attributed to drug use (Webster & Freeman 2001). It is likely that the use of CMs in Western countries is a far less important factor.

CRITICAL PERIODS IN HUMAN DEVELOPMENT

The safe use of any medicine in pregnancy must take into account the safety of the treatment to be used, the seriousness of the patient's presenting problem and the timing of exposure.

In the first two weeks, prior to implantation, an insult is thought to have an all-or-nothing effect. Assuming the embryo survives, the risk of structural malformations to the fetus is greatest 17–70 days post-conception, a critical stage of organ development (Freyer 2008). After this time, organs continue to mature, so later adverse effects tend to be functional rather than structural and major birth defects are unlikely. Functional defects are less obvious than structural ones and may become obvious only when the child is older. The central nervous system, eyes, teeth and external genitalia are the last organs to fully develop and continue to mature until the baby reaches full term.

If practitioner and patient agree that medicinal treatment is warranted, then minimising exposure during critical developmental times (Fig 11.1) is essential. This means using the lowest effective dose of the least toxic substance for the shortest period of time.

TERATOGENESIS

Teratogens are agents that result in structural or functional defects in the development of fetal organs (Shehata & Nelson-Piercy 2000). Sources of exposure to these agents include: contaminated air, water, soil, food, beverages, household items, and medicines (including CMs) (Kovacic & Somanathan 2006). Teratogens can cause a variety of effects, including embryo/fetal death, intrauterine growth restriction and increased risk of malformations and carcinogenesis (Shehata & Nelson-Piercy 2000). The exact mechanisms responsible for teratogenicity are unknown but theories include damage to DNA, membranes, protein and mitochondria, enzyme inhibition and hormonal interference (Kovacic & Somanathan 2006). Despite the potential for teratogens to have devastating consequences, only a relatively small number of fetuses exposed to these agents experience adverse effects (Freyer 2008). This relates to factors such as the dose and duration of exposure, genetic susceptibility of the fetus/embryo, timing of exposure, specific mode of action of the teratogen (Miller et al 2007) and nutritional and disease status of the mother–baby unit (Shehata & Nelson-Piercy 2000).

Data on herbal teratogens is limited and largely based on animal studies, which are not completely reliable. Blue cohosh is an example of a herb for which there is some evidence to suggest a potential teratogenic effect, based on animal studies (Keeler 1976, Keeler et al 1976, Kennelly et al 1999). Other herbs that may increase the risk of fetal malformations (predominantly based on limited animal data) include aloe, andrographis, cat's claw, Jamaica dogwood, pau d'arco, pennyroyal, poke root, tribulus and white horehound (Mills & Bone 2005). There is very little evidence of teratogenic activity or adverse pregnancy outcomes from the use of nutritional supplements, with the notable exception of high-dose vitamin A. Interestingly, deficiencies of nutrients such as vitamin A, folate, vitamin B_{12}, vitamin D, iodine and zinc have been found to have adverse effects that include teratogenesis, emphasising the important role these nutrients have in normal embryonic and fetal development.

Neonatal withdrawal

While the fetus is in utero, the placenta supplies it with nutrients and other substances, as well as drugs. When the baby is born, placental supply ceases, which can lead to neonatal withdrawal syndromes for certain drugs such as beta-blockers, SSRIs and other antidepressants, opiates and alcohol (Freyer 2008, Sanz et al 2005). It is not known whether the use of CMs during the final trimester can also induce withdrawal syndromes.

HOW IS SAFETY EVALUATED IN PREGNANCY?

One of the hardest challenges a clinician faces is advising a pregnant patient about the safety of a treatment. A key factor to consider is the strength of evidence indicating the treatment is safe or, as so often happens in pregnancy, the lack of evidence indicating it is unsafe. More specific factors are the dose of medicine to be used, precise timing of exposure and duration of exposure.

When evaluating the effectiveness of a treatment, prospective randomised trials and

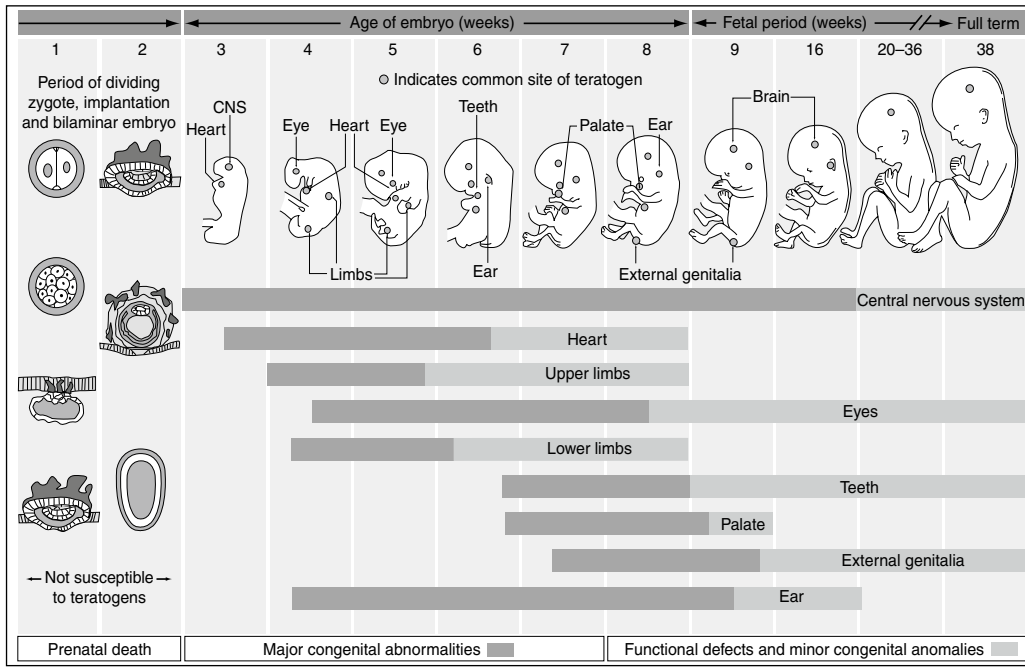

FIGURE 11.1 Critical periods in human development (From Moore KI, Persaud TVN. The developing human: clinically oriented embryology, 6th edn. Philadelphia: WB Saunders, 1998, p 548. With permission.)

meta-analyses are widely considered the gold standards. When evaluating safety in pregnancy, there is a paucity of such trials because pregnant women tend to be excluded, so other methods of information gathering are required. Epidemiological studies, tests with animal models, post-marketing surveillance systems, case reports and traditional use provide the main inputs into establishing safety, but each method has limitations and should not stand alone without corroborating evidence from another source.

Epidemiological studies

Epidemiological studies are also known as population studies. Owing to their large participant numbers, epidemiological studies can detect large and small size effects and sometimes rare outcomes, if the study population is sufficiently large and follow-up is sufficiently complete. As such, they may provide useful information regarding safety in pregnancy.

Considering the incidence of fetal malformations is already small (2–4%), extremely large participant numbers would be required to detect a slight increase above what may normally be expected. For example, a study would require 35,000 women in order to establish with a 95% confidence level that a medicine changes the naturally occurring frequency of a congenital malformation by 1% (Lee et al 2000). Unfortunately, most epidemiological studies have inadequate statistical power to detect this outcome because they lack sufficient patient numbers. This means that no medicine (pharmaceutical or complementary) has proven safety based on reliable epidemiological data involving sufficient numbers of women.

Animal studies

Animal studies of reproductive toxicity are required for all new drugs before they are licensed, but they are not required for CMs. While they can provide some assurance of safety, animal tests have limited usefulness because results do not always extrapolate accurately to humans. The problem of false positives is more common than false negatives, whereby medicines that produce defects in animals are later found to be relatively safe in humans (e.g. corticosteroids) (Lee et al 2000). It is likely that the excessive doses used in testing increase the risk of producing a false positive, as there is greater embryonic and maternal exposure to the medicine than would be expected in clinical practice. This should be kept in mind when interpreting the results of drug or herbal medicine testing in animal models.

Post-marketing surveillance systems

In many cases, more meaningful safety data becomes available only when a medicine is in widespread use and women knowingly

or inadvertently take it during pregnancy. Those medicines with high effect rates will be detected more quickly than less potent teratogens. For example, the teratogenic effect of isotretinoin was detected about one year after it came onto the market, whereas the antiepileptic drug valproic acid was available in Europe in the 1960s yet it took approximately 20 years of use by millions of women before its teratogenic potential was identified (Webster & Freeman 2001).

Post-marketing surveillance systems are set up to detect unfavourable outcomes and highlight adverse events rather than establishing safety, an inherently more difficult endpoint.

Adverse event case reports

Adverse event case reports are an account of an individual's suspected response to a treatment. Case reports are notoriously unreliable, as they tend to lack sufficient detail to clearly establish causality and fully eliminate the influence of confounding factors. Individual case reports become more convincing when a series of similar reports are collected.

Several factors should be considered when interpreting a case report; firstly, did the exposure to the medicine happen at the appropriate critical stage in pregnancy (usually first trimester) and was the dose used clinically relevant and similar for all cases? Additionally, if a complementary medicine is implicated, has the medicine been tested for contaminants and adulteration to exclude extrinsic factors and did the treatment involve a single entity or combination therapy (the norm in complementary medicine)? Finally, the traditional body of evidence that accompanies herbal medicines may provide further insights when interpreting cases.

The following three cases are presented as examples of the literature. They involve the herbs dong quai, Korean ginseng and blue cohosh. The reports indicate a probable link between herbal use and adverse outcome; however, none of the products implicated were tested for herbal authenticity or for the presence of contaminants or adulterants, an essential step towards drawing a definitive conclusion.

Case report 1

A 32-year-old woman, three weeks postpartum, developed acute headache, weakness, light-headedness and vomiting, with a blood pressure reading of 195/85 mmHg (Nambiar et al 1999). She reported using dong quai for postpartum weakness and had not been taking any other medicines. Her three-week-old son's blood pressure was also raised at 115/69. Within 48 hours of stopping herbal treatment, blood pressure normalised for both the mother and the breastfed child.

Case report 2

In 1990, a case report published in JAMA described a 30-year-old mother who had taken *Panax ginseng* (650 mg twice daily) throughout pregnancy and during lactation of her two-week-old baby (Koren et al 1990). The boy was noted to have signs of androgenisation, thick black pubic hair, hair over the entire forehead, swollen, red nipples and enlarged testes. After 2 weeks, his pubic and forehead hair began to fall out and was scant by 7.5 weeks. Excessive androgen production was ruled out and the authors suspected the effects were produced by hormonal activity of the herbal treatment. Letters to the editor were subsequently exchanged suggesting the product contained Siberian ginseng and not *Panax ginseng* (Awang 1991). The story does not end here, because Siberian ginseng has no significant androgenic activity in vivo that could account for the effects observed (Awang 1991, Waller et al 1992). It is now suspected that the herbal product did not contain Siberian ginseng but instead *Periploca sepium* (called wu jia or silk vine), as US herb companies importing Siberian ginseng from China have been known to be supplied with two or three species of *Periploca* (Awang 1991).

Case report 3

A newborn infant presented with acute myocardial infarction associated with profound congestive heart failure and shock (Jones & Lawson 1998). The mother had been ingesting blue cohosh (*Caulophyllum thalictroides*) in the month prior to delivery to facilitate the birthing process. She had been instructed to take one tablet daily but elected to take three times the recommended dose in the 3 weeks before delivery. During this time she noticed an increase in uterine contractions and a decrease in fetal activity. The infant eventually recovered after being critically ill for several weeks. Attending doctors excluded other causes of myocardial infarction and indicated that blue cohosh was responsible for the adverse event. On late follow-up at 2 years of age the child is doing well with good exercise tolerance, and

normal growth and development. However, cardiomegaly persists, left ventricular function remains mildly reduced, and he still receives digoxin therapy.

Clinical studies

While prospective clinical studies of herbal safety in pregnancy are problematic, retrospective studies are easier to conduct. Establishing cause–effect relationships beyond reasonable doubt is rare because of the myriad of confounding factors present; however these studies may identify common or palpable problems that could be investigated in appropriate models.

Example: echinacea

A Canadian study involving 412 pregnant women investigated the safety of echinacea in pregnancy (Gallo et al 2000). These women had contacted a teratogen information service (Motherisk Program) between 1996 and 1998 with concerns about the safety of ingesting echinacea during pregnancy. Half the group had already taken the herb, whereas the others decided against use and so were enrolled as a control group. Of the 206 women in the echinacea group, 112 (54%) used the herb in the first trimester and 17 (8%) used it throughout their pregnancies. No significant differences were seen between the groups for rates of major and minor malformations or any pregnancy outcome including delivery method, maternal weight gain, gestational age, infant birth weight or fetal distress.

Long-term use

Long-term use of a medicine by large populations of women without apparent increase in adverse events is considered to contribute towards evidence of safety. For example, the Australian Drug Evaluation Committee (ADEC) has classified the drug metoclopramide as relatively low risk because the 'drug has already been taken by large numbers of pregnant women and women of child-bearing age without proven increase in fetal harm' (Bryant et al 2003).

With regard to herbal medicine, 'long-term use' may actually refer to hundreds or even thousands of years of use, not just decades as is the case with pharmaceutical medicines. In fact, many herbal medicines such as ginger and garlic have been used as both foods and medicines since antiquity. This has allowed a large body of longitudinal and retrospective evidence to accumulate, which gives herbalists an extra dimension to consider.

Like all forms of evidence, traditional evidence has its limitations and must be interpreted carefully. It is likely that traditional healers would have found it easier to identify poisonous herbs and herbs that induce acute or obvious adverse effects than those that induce insidious, rare or delayed-onset adverse outcomes. There may also be significant differences in the way a herbal medicine is grown, prepared and used today compared with the practice in former times, thereby allowing larger doses to be taken and different herbal constituents to be absorbed (Tannis 2003).

WEIGHING UP THE EVIDENCE

For both pharmaceutical and complementary medicines, the evidence base is incomplete and insufficient to state with certainty that any medicine is safe in pregnancy. To build a case for safety, evidence from multiple sources must be considered to fill in as many gaps in knowledge as possible.

In the case of complementary medicines, any evidence supporting or contraindicating use during pregnancy must be based on the totality, quality and relevance of the evidence. In general, the greater the consistency of evidence from different sources, the stronger the evidence is overall.

In Australia, the ADEC has classified drugs on their potential to cause harm during pregnancy (Table 11.2, p 164). Eight categories are possible and each describes the evidence used to indicate safety or lack of safety. They rely on evidence gathered from animal models and post-marketing surveillance systems, and also consider the proven, suspected or expected potential of a drug to cause adverse outcomes (e.g. cytotoxic drugs).

Proposing a different system for complementary medicines

A similar grading system is required for complementary medicines, building a case for safety or harm based on considering multiple forms of evidence. Ideally, the new system should take into account the availability and credibility of various traditional evidence sources and the relative lack of data available from animal studies. It should also take into account the relative safety of over-the-counter complementary medicines in comparison to scheduled pharmaceutical drugs, and whether the association between exposure and proposed adverse outcome is biologically plausible.

TABLE 11.2 ADEC Pregnancy Categories (Australia)

Category	Description
A	Drugs that have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the fetus having been observed.
B1	Drugs that have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage.
B2	Drugs that have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage.
B3	Drugs that have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.
C	Drugs that, owing to their pharmacological effects, have caused or may be suspected of causing harmful effects on the human fetus or neonate, without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.
D	Drugs that have caused, are suspected to have caused or may be expected to cause an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.
X	Drugs that have such a high risk of causing permanent damage to the fetus that they should not be used in pregnancy or when there is a possibility of pregnancy.

Note: Based on ADEC 1999. For drugs in the B1, B2 and B3 categories, human data are lacking or inadequate and subcategorisation is therefore based on available animal data. The allocation of a B category does *not* imply greater safety than the C category. Drugs in category D are *not* absolutely contraindicated in pregnancy. Moreover, in some cases the D category has been assigned on the basis of suspicion.

The following examples are provided to give the reader some suggested questions to ask of the evidence and the types of evidence available to consider when evaluating safety in pregnancy.

Zingiber officinalis *(ginger)*

- Is traditional evidence available about the substance in general? — *Yes*
- Does traditional evidence caution or contraindicate against use in pregnancy? —*Yes*
- Is the reason for the traditional caution or contraindication biologically plausible? — *No*
- Is scientific evidence available in general about the substance? — *Yes*
- Does scientific evidence (from human or animal studies) provide information about pharmacological effects that may be of concern in pregnancy? — *Yes*
- Are there any studies suggesting that the substance may be safe in pregnancy? — *Yes*

Traditionally used as an antiemetic, ginger has encouraging research to support its use during pregnancy for nausea and vomiting (Borrelli et al 2005). No adverse effects have been reported in several studies examining ginger in the treatment of nausea and vomiting in pregnancy.

A systematic review of four double-blind RCTs (n = 449) and one prospective observational cohort study (n = 87) evaluated the effects of ginger on pregnancy outcomes. The preparation used in the trials was a ginger root powder or extract, taken 3–4 times daily (total dose ranged from 1.0–1.5 g) from 8 to 20 weeks' gestation. No dose was provided in the prospective study. No difference in the occurrence of spontaneous abortions, stillbirth, term delivery and caesarean deliveries, neonatal death, gestational age or congenital abnormalities was found between women who took ginger compared to those who took vitamin B_6 or a placebo, or to the general population (Borrelli et al 2005).

Unfortunately there is a lack of consensus regarding the safety of ginger during pregnancy. Soudamini et al (1995) suggest ginger contains possible mutagenic properties, but this effect appears to be counteracted by zingerone, another constituent present in the whole rhizome (Nakamura & Yamamoto 1982). Traditionally, ginger has been contraindicated in labour due to the possibility of increased postpartum haemorrhage, and in large doses ginger is traditionally thought to act as an emmenagogue (Grieve 1971). German Commission E

suggests that ginger is contraindicated in pregnancy, while more recent research suggests that doses up to 2 g/day of dried ginger root have been used safely. When considered in a comparison of recent research, the proposed notion of haemorrhage is unlikely (Lumb 1994). Even in very large doses (ginger tea up to 50 g/L), ginger had no impact on maternal toxicity or fetal malformations in an animal model, but embryo losses were double compared to the controls. No evidence of maternal toxicity was found for a patented extract of ginger (EV.EXT 33) given in doses of up to 1000 mg/kg/body weight daily to pregnant rats during the period of organogenesis (Weidner & Sigwart 2001).

Rubus ideaus *(Raspberry leaf)*

- Is traditional evidence available about the substance in general? — *Yes*
- Does traditional evidence caution or contraindicate against use in pregnancy? — *No*
- Is scientific evidence available in general about the substance? — *Yes (limited)*
- Does scientific evidence (from human or animal studies) provide information about pharmacological effects that may be of concern in pregnancy? — *Yes*
- Are there any studies suggesting that the substance may be safe in pregnancy? — *Yes*

Raspberry leaves appear to have a dual effect on the uterus, acting as both a stimulant and a relaxant to the uterine musculature (Bamford et al 1970). The use of this herb in concentrated form is traditionally recommended only in the second and third trimesters owing to its possible effects on the uterus. Traditional evidence and select pharmacological studies highlight that this herbal medicine has an effect on uterine contractions (Bamford et al 1970). Unfortunately, there is little research on either the efficacy or the safety of raspberry leaf. Two clinical studies evaluating the safety of raspberry leaf in pregnancy have reported no evidence of toxicity in either mother or child (Parsons et al 1999, Simpson et al 2001), although evidence from older animal studies is less clear (Burn & Withell 1941, Whitehouse 1941).

PART 3: ADVISING PATIENTS IN CLINICAL PRACTICE

At some stage of practice most clinicians have to consider the question, 'Is this treatment safe in pregnancy?' The answer to such a question is never straightforward, as establishing safety in pregnancy with any degree of certainty is difficult, partly because scientific methodologies to assess safety are inexact, the evidence base is incomplete and probably will remain so, and because birth defects occur spontaneously in 2–3% of all pregnancies for no known reason.

Over the years medical practitioners and pharmacists have generally held the view that all medicines should be avoided during pregnancy, where possible. This has referred to the use of pharmaceutical medicines and is wise counsel. With the increasing popularity and accessibility of complementary medicines, many have extended this caution to include herbal medicines under the assumption that the same safety issues apply. Indeed, the safety issues are similar and prudence is still required.

Naturopaths and herbal medicine practitioners hold a more targeted view and recommend a small number of herbal and nutritional medicines during different stages of pregnancy, while being mindful of many others that are considered to be contraindicated for various reasons.

Moving ahead, it is easy for clinicians to adopt the conservative view that all herbal medicines should be avoided throughout pregnancy. This is not useful in practice, however, especially as women will continue to take them in the belief that they are safe. In fact it could be argued that best practice means considering all treatment options for safety and efficacy in pregnancy, including herbs and natural supplements.

When medicinal treatments present unacceptable risks or are ineffective, complementary medicine as a treatment domain offers a broad range of non-medicinal treatment options that can be considered by clinicians. For instance, lifestyle prescriptions, dietary manipulation, massage, acupuncture and aromatherapy provided by appropriately trained practitioners can address a range of symptoms during this sensitive time.

FACTORS TO CONSIDER IN PRACTICE

It has been estimated that in the United States up to 50% of pregnancies are unplanned and about 5–10% of women are pregnant at any one time (Webster & Freeman 2001). As such, a large proportion of women may not be aware they are pregnant until well into their first trimester. This raises many issues regarding safety, as it is possible for a woman to be taking a complementary medicine during this period and potentially placing the fetus and pregnancy at risk. In Australia, the allocation of an AUST L

PRACTICE TIPS
GENERAL RULES FOR USING CMs IN PREGNANCY

- Use complementary medicine within the Quality Use of Medicines (QUM) framework.
- Consider the patient's presenting health status and comorbidities.
- Consider non-medicinal treatment options where appropriate. Is such a treatment available and likely to be successful?

Risk–benefit analysis

- If a complementary medicine is under consideration, what are the potential risks and benefits to the mother and fetus?
- What are the risks and benefits (to each) of not prescribing?

Timing of intervention

- Avoid all medicinal agents where possible, especially in the first trimester.
- Carefully consider the timing of the intervention in regards to gestational age of the fetus: the susceptibility of a fetus to toxic effects changes throughout gestation.
- Consider appropriate dose, dose frequency and duration of treatment.

Pharmacotherapy compared with complementary medicine

- If the patient's condition is sufficiently severe that pharmacotherapy is being considered, then clinicians should consider whether an appropriate complementary medicine treatment exists with lower risk of harm.
- If clinician and patient decide a complementary medicine is to be used, then the lowest possible dose should be used for the shortest period of time.
- CM is best prescribed by a qualified and appropriately trained health professional.

Counselling

- Counsel pregnant women to avoid exposure to unnecessary medicines and chemicals.

Education and communication

- If use of a complementary medicine is being considered, an open discussion about the potential benefits and potential risks must ensue, so that patients can make an informed decision. This includes providing information about what is known about the safety of the treatment and what remains unknown.
- Communication is essential between all health professionals involved in obstetric patient management and the patient.
- Encourage patients to disclose complementary medicine use to all health professionals in their obstetric team.

Special caution should be exercised with women due to have an elective caesarean section or other surgery. Presurgery recommendations should be considered.

ADDITIONAL RULES: TRADITIONAL UNDERSTANDING OF SAFE HERBAL USE IN PREGNANCY

- Avoid all known toxic and poisonous plants at all times, such as aconite, pennyroyal, tansy.
- Avoid all thujone-containing herbal medicines, such as *Achillea millefolium* (yarrow), *Thuja occidentalis* (thuja) or *Artemisia absinthium* (wormwood)
- Avoid internal use of pure volatile oils from herbal medicines, especially during the first trimester. Herbal teas and small concentrations of oils used as flavouring are the exception (e.g. peppermint oil or food quantities of essential oil containing herbal medicines).
- Avoid emmenagogue herbal medicines in the first trimester and use only under professional supervision at later stages.
- Herbs used to assist delivery should be used only under close professional supervision in the final 6 weeks of pregnancy.

number to an over-the-counter (OTC) product denotes general safety, even when taken without professional advice. Theoretically, it means all OTC-listed products should also be safe in pregnancy, but this remains to be established. To safeguard patients, it is recommended that all practitioners who wish to prescribe medicines with questionable safety in pregnancy should consider the risks in relation to possible benefits and discuss all safety concerns.

Individual prescribing

The decision to prescribe or withdraw a complementary medicine must be made on an individual case-by-case basis. The safe use of any medicine in pregnancy must take into account the safety of the treatment being considered, the seriousness of the patient's presenting problem, maternal age, gestational age of the fetus and timing of exposure. This includes a consideration of the dose to be used, dosing

interval and timing in respect to other medicines and food. Additionally, the patient's presenting health and nutritional status, comorbidities, kidney and liver function and personal attitude to treatment are important factors.

If practitioner and patient agree that a medicine is to be used, steps should be taken to reduce harm, such as recommending the lowest effective dose for the shortest period possible. While special cautions exist for the first trimester, care must be taken at all stages of pregnancy, as fetal growth and development continues for the full period of gestation.

Timing of the intervention

In practice, choosing the correct dose and administration form is essential, and in pregnancy there is the additional consideration of correct timing, which is important for achieving a desired clinical result with a minimum of risk. For example, folate supplementation has been shown to prevent neural tube defects when administered in the preconception period and continued during the first trimester (Berry et al 1999). Similarly, antioxidant supplements appear to be ineffective in reducing preeclampsia when started later in pregnancy (Rumbold et al 2008); however, positive results in preeclampsia were reported in a study that commenced treatment in the first trimester with a broad spectrum antioxidant supplement (including vitamin A 1000 IU, vitamin C 200 mg, vitamin E 400 IU, folic acid 400 mcg, selenium 100 mcg, zinc 15 mg, copper 2 mg, N-acetyl cysteine 200 mg, iron 30 mg) (Rumiris et al 2006).

Informed consent

Evidence-based patient-centred care means that all clinicians are required to present risk/benefit information to their patient, who can then make an informed choice. This means an honest discussion between patient and practitioner about what is known and what remains unknown about the safety and efficacy of a treatment. Patients will no doubt vary in their interest and ability to comprehend and recall the necessary information, so written information and assurance that the woman understands the issues during the time of consultation is useful.

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CHAPTER 12
INTRODUCTION TO WELLNESS

WHAT IS 'WELLNESS'?

'Wellness' is a concept that has gained popularity in recent years but still has no rigorously developed definition, theory or philosophy. At a very simple level, wellness can be equated with health which, according to the World Health Organization, is 'a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity' (WHO 1948). Wellness, however, can also be seen as distinct from health in that it is holistic and multidimensional. The notion of wellness includes not only physical, mental and social dimensions, but also emotional, cultural, spiritual, educational, sexual, occupational, financial, environmental, ethical and existential dimensions, with the assumption being that if any one of these dimensions is deficient, complete wellness cannot be achieved.

Wellness describes a quality of systems rather than isolated entities and, as such, it is dependent on relationships and must take into account both content and context. Because it describes systems, the notion of wellness can be applied to individuals as well as to communities, businesses and large-scale economies. The notion of wellness requires an ecological perspective that can be expanded to include the concepts of human security, corporate social responsibility, social justice, environmental impact and sustainability, together with subjective fulfilment and wellbeing.

In 1961, wellness pioneer Halbert Dunn defined wellness, in his book *High-level wellness*, as 'an integrated method of functioning which is oriented toward maximizing the potential of which the individual is capable' (Dunn 1961, p 4). He acknowledges that wellness is dependent on the relationship between individuals and their environment, stating that wellness 'requires that the individual maintain a continuum of balance and purposeful direction within the environment where he is functioning'. He also stated that 'wellness is a direction in progress toward an ever-higher potential of functioning' (Dunn 1961, p 6).

More recently the [US] President's Council on Physical Fitness and Sports proposed a uniform definition of wellness as 'a multidimensional state of being describing the existence of positive health in an individual as exemplified by quality of life and a sense of well-being' (Corbin & Pangrazi 2001). Yet another definition suggests that wellness is an 'active process of becoming aware of and making choices toward a more successful existence' (US National Wellness Institute 2009). Another proposed definition is:

> Wellness is the multidimensional state of being 'well', where inner and outer worlds are in harmony: a heightened state of consciousness enabling you to be fully present in the moment and respond authentically to any situation from the 'deep inner well of your being'. Wellness is dynamic and results in a continuous awakening and evolution of consciousness and is the state where you look, feel, perform, and stay 'well' and, therefore, experience the greatest fulfilment and enjoyment from life and achieve the greatest longevity. (Cohen 2008a, p 8)

This definition implies that the state of wellness allows the greatest flexibility to respond to situations and therefore provides the greatest resilience to stress and disease. Wellness in this context can be seen as the best preventative medicine. In this definition wellness is also seen as a state of consciousness that guides the quality of our relationships with the world and therefore cannot be viewed separately from the environment in which it occurs. Thus, if 'health' is 'wholeness', then wellness is the experience of an ever-expanding realisation of what it means to be whole (Cohen 2008a).

Travis and Ryan suggest that wellness is never a static state but rather a way of life, and that wellness and illness exist along a continuum: just as there are degrees of illness, there are also degrees of wellness. Travis and Ryan further see wellness as a choice, a process, a balanced channelling of energy, the integration of body, mind and spirit, and the loving acceptance of self (Travis & Ryan 2004).

If health and disease are considered to be at opposite ends of a spectrum, then it is possible to classify health into three broad areas: ill health (illness), average health and enhanced health (wellness) (Fig 12.1). The divide between ill health and average health is generally defined in Western medical terms, which classify diseases based on symptom patterns or other diagnostic parameters. Western medicine uses a bottom-up approach that aims to define and understand illness, and develop interventions such as drugs and surgery to treat or prevent the disease and control factors that reduce wellbeing ('stressors').

The divide between average health and enhanced health is less distinct. Enhanced health is more than just being disease-free: it assumes high levels of physical strength, stamina and mental clarity, as well as physical beauty and maximal enjoyment and fulfilment from life. This requires the holistic integration of multiple factors that determine physical, psychological, emotional, social, economic, environmental and spiritual health. In many Eastern philosophies, the idea of enhanced health can be extended to the concept of 'perfect health' or 'enlightenment', whereby a person is 'at one with the universe' and hence in a state of perfect bliss or 'nirvana' (Cohen 2003).

Moving up the spectrum from illness to wellness allows for greater flexibility of response and hence greater resilience; the best form of prevention is therefore to be as high on the spectrum as possible. Thus, while 'stressors' tend to reduce the ability to respond and create downward movement, upward movement can be facilitated by 'blissors', which create greater wellbeing. Throughout the spectrum, however, there is also a central axis that represents the core of our being. This central core, which may be termed the 'soul' or the 'essence', is an eternal and immortal aspect of the self that is naturally at one with the universe and blissful.

Bliss, or 'ananda' in Sanskrit, is considered by Vedic scholars to be the innermost level of the individual self, as well as the nature of the whole universe. It is the goal of the path to enlightenment and is found in the deepest experience of meditation and the innermost level of our being (Maharishi 1957–64). Bliss is also the ultimate aim of Eastern healing and spiritual practices, which adopt a top-down approach by attempting to elicit bliss through meditation and other practices that enhance wellbeing ('blissors') (Cohen 2008a).

The state of bliss can also be considered as the ultimate in achieving human potential. As the late anthropologist Joseph Campbell states:

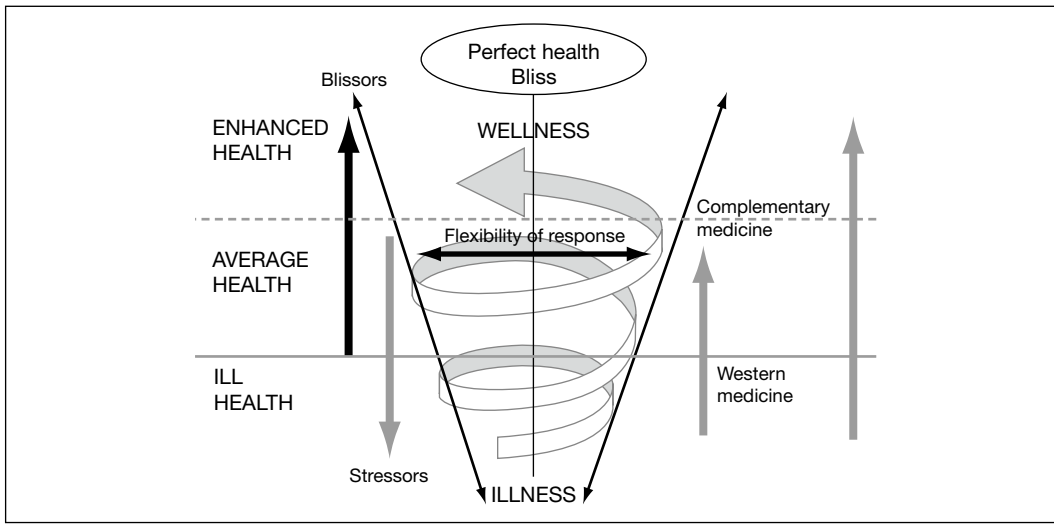

FIGURE 12.1 The illness–wellness spectrum (Cohen 2008a)

> I think that most people are looking for an experience that connects them to the ecstasy of what it could feel like to be totally alive. To know the unburdened state of total aliveness is the pinnacle of the human potential. (Campbell 1988)

This 'state of total aliveness' is what many people may consider to be 'wellness'.

THE WORLD IN CRISIS

It seems that all people at some time have tried to tackle the question of how to live well in the world. This single question has driven many different areas of human endeavour and has led to innovations that have created new technologies and ways of living that have allowed human populations to expand exponentially (Meadows et al 1976).

The world is currently facing a series of crises that are challenging the financial system, the climate and the environment. Increased global terrorism, pandemics, environmental pollution, general toxicity and natural disasters are breaching national boundaries and threatening human security. We also currently live in a world where one-third of the world's population is dying from diseases linked to malnutrition and starvation; another third is dying from obesity and diseases related to overconsumption; toxic chemicals are continuously being created and released into our environment and food supply, and people are becoming increasingly disconnected from their natural environment and one another.

Modern healthcare systems are also struggling to provide quality care to all in need, as the burden of illness-care reaches barely manageable proportions. It is becoming clear that the current illness-based medical model is not sustainable and is ill-equipped to meet the needs of the global population or deal with the consequences of an ageing population, increasing healthcare costs and an epidemic of lifestyle-related diseases such as obesity, diabetes, heart disease and cancer.

The disproportionate focus on illness has allowed unhealthy lifestyle practices to remain largely unchecked, thereby allowing them to expand across the globe to the point where they now represent the greatest threat to human health and survival. A 2005 report by the World Health Organization entitled *Preventing chronic disease: A vital investment* estimates that of the 58 million deaths in the world in 2005, 35 million (60%) were caused by chronic diseases such as heart disease, stroke, cancer, chronic respiratory diseases and diabetes. The report goes on to suggest that 80% of premature heart disease, stroke and type 2 diabetes and 40% of all cancers are preventable, concluding that the main modifiable risk factors for these diseases are lifestyle-related and include unhealthy diets, physical inactivity and tobacco use (WHO 2005).

It has been predicted that, as a result of unhealthy lifestyles, for the first time in history the lifespan of the next generation in the United States could be shorter than that of their parents (Olshansky et al 2005). In a PriceWaterhouseCoopers (PWC) report on the future of healthcare entitled *HealthCast 2020: Creating a sustainable future* (PWC 2005), it is suggested that 'There is growing evidence that the current health systems of nations around the world will be unsustainable if unchanged over the next 15 years' (PWC 2005, p 2), while 'preventive care and disease management programs have untapped potential to enhance health status and reduce costs' (PWC 2005, p 4).

IN SEARCH OF WELLNESS

It is becoming increasingly evident that the fate of all people is ultimately linked and that as a global species we must find sustainable ways to live well in the world together. It could be viewed that humanity has reached a 'tipping point', bringing the possibility of either substantial hardship or a breakthrough into new ways of living and a new phase in human evolution. This new phase represents a culmination of thousands of years of human history, during which different philosophies, traditions and technologies have attempted to address the questions of life, ageing, illness and death.

The search for wellness is a common goal for all people. It can be understood as a conscious extension of the basic animal instinct to avoid pain that has its origins at the dawn of humanity when consciousness first became self-reflective (Cohen 2000). This search has influenced the evolution of medicine, which has seen the elaboration of two distinct yet complementary approaches: Eastern medicine, which is based on holistic thinking that maintains a cosmological and systems perspective outlining a philosophy of life; and Western medicine, which is based on a reductionist approach, emphasising controlled scientific experimentation and mathematical analysis (Cohen 2002).

The different health paradigms that aim to improve health and wellness have attempted to address the same issues in different ways. The principle of consilience suggests that there is an underlying unity of knowledge whereby a small number of natural laws may underpin seemingly different conceptual frameworks (Wilson 1999). Indeed there are general concepts and principles that seem to recur as themes across different healthcare paradigms.

THE THERMODYNAMICS OF WELLNESS

Perhaps the most ubiquitous principle in medical thought is the idea that life is dependent on energy. The science of energy is well described in the field of thermodynamics, which proposes universal laws that give rise to precise mathematical equations that form the foundation for modern science and technology. However, while the field of thermodynamics purports to describe all energetic processes, it is seldom applied directly to the fields of health and medicine, despite 'energy' being a basic principle in virtually every healing tradition.

The concept of energy is described in different traditions as 'life energy', 'vital force', 'prana', 'chi' (or 'Qi'), and is said to flow along defined pathways and support the functioning of living systems. Traditional Chinese medicine has developed a sophisticated framework for conceptualising this energy: it is seen to encompass the concept of 'flow' and to move according to the dynamic interplay of the opposite yet complementary forces of 'yin' and 'yang', which guide the process of transformation whereby non-living things become animate. In this view, pain and disease are said to result when the energetic flow is disrupted, and healing is aimed at restoring the natural balance and flow (Cohen 2002).

As science does not recognise a form of energy specific to living systems, many concepts underlying Eastern medicine have been criticised as unscientific. There are parallels, however, between Eastern and Western concepts, which can be seen to be linked through the concept of information. Information can be measured in terms of energy or 'joules/degree Kelvin' (Tribus & McIrvine 1971), and there is a congruence between the concepts of 'Qi' in Eastern medicine and 'information' in thermodynamics.

Thus the Eastern concept of disease arising from a blockage of 'Qi' can be seen to parallel the second law of thermodynamics, which describes a tendency towards disorder or entropy in an isolated system. Disease and the adverse effects of ageing, which include progressive degeneration of tissues together with loss of function, can therefore be related to an increase in entropy as a consequence of blockages or isolation of different systems. In contrast, the ability of living systems to grow, evolve and learn appears to defy the second law and can be related to an open exchange between organisms and the environment. This can be extended to the concept of 'nirvana', or perfect bliss, whereby a person is 'at one with the universe' and there is no distinction between self and non-self, thus creating an open system that is no longer prone to the increase in entropy that occurs in isolated systems (Cohen 2002).

WELLNESS AND FLOW

While it may be true that life depends on energy, living systems must remain 'open', as it is the flow of energy through them that maintains their integrity. The concept of 'flow' is a powerful one that provides a bridge between Eastern and Western thought. The concept of flow applies to both thermodynamic processes and systems theory, as well as to the cyclic thinking of Eastern medicine. The concept of flow has also been applied to subjective psychological states that involve the integrated functioning of mind and body. This concept has been developed by Mihalyi Csikszentmihalyi who describes flow as 'a joyous, self-forgetful involvement through concentration, which in turn is made possible by a discipline of the body' (Csikszentmihalyi 1992).

The state of flow occurs when perceived challenges exactly match the skills and capacity to respond. Such a state is therefore a 'whole of consciousness' phenomenon that requires the integrated action of both physiological and psychological processes, and hence the involvement of the entire being. In requiring 'wholeness', the 'flow state' is aligned with health and wellness, and engenders positive feelings that include:

- being completely involved in what we are doing — focused, concentrated
- a sense of ecstasy — of being outside and beyond everyday reality
- great inner clarity — knowing what needs to be done and how well we are doing it (introspective, realistic feedback)
- knowing the activity is able to be done — that our skills are adequate to the task

- a sense of serenity — having no undue concerns or worries about oneself, and a feeling of growing beyond the boundaries of the ego
- timelessness — being thoroughly focused on the present so that hours seem to pass by in minutes
- intrinsic motivation — whatever produces flow becomes its own reward (Csikszentmihalyi 2004).

The idea that positive psychological states and wellbeing require 'open systems' is recognised in everyday common language in the phrases 'having an open heart' or 'open mind'. The concept of flow sustaining life is also a basic tenet of Chinese and other traditional medicine philosophies. A thermodynamic model that includes the concept of energy and flow can also be seen to include many parallels between Eastern and Western concepts and thus provide links between different conceptual systems (Fig 12.2).

For example, the process of flow leading to transformation and the maintenance of living systems parallels the concept of the five elements or phases of transformation that is common to Chinese medicine, Ayurvedic medicine and ancient Greek medicine (which considered quintessence as a fifth element in addition to air, water, fire and earth). The result of this transformation is represented by the concept of 'yin' and 'yang', which refers to interdependent yet mutually exclusive opposites and can be compared to the concept of 'complementarity' in quantum physics or the concept of homeostatic balance in physiology. The result of this balance leads to an increase or decrease in order as described by entropy or evolution, while the infinite nature of direct experience can be compared to the concept of 'Tao' or the mathematical concept of 'absolute infinity', both of which are defined as being inherently incomprehensible (Cohen 2002).

WELLNESS METRICS

Wellness is holistic and multidimensional, and involves content and context. As such it is both subjective and objective, and is difficult to quantify. As yet there are no agreed upon metrics by which wellness can be reliably measured, despite the existence of many potential indicators and proxy measures that may be applied to populations as well as individuals. Thus it is now possible to measure subjective states such as 'quality of life', 'happiness' and 'wellbeing' through instruments such as the Australian Quality of Life Index (Cummins et al 2008), as well as to use more objective and physiological measures such as anthropometric and biometric data. Objective indicators of wellness can also be obtained from tissue

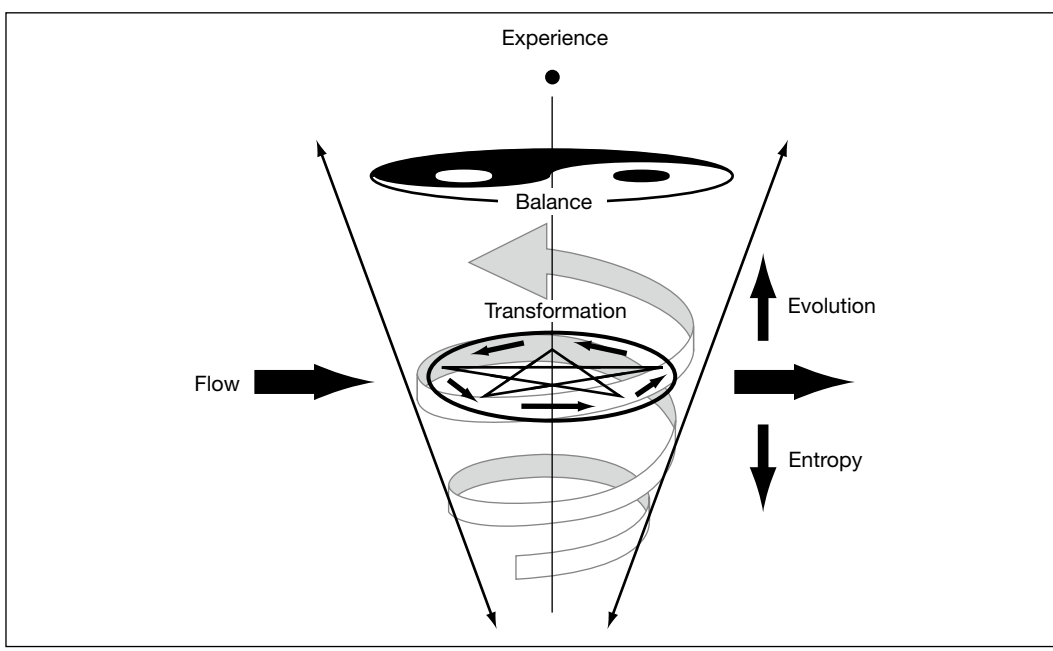

FIGURE 12.2 Pictorial conceptualisation of wellness concepts from traditional Chinese medicine (Cohen 2008a)

sampling and measuring biochemical, hormonal, genetic, haematological and toxological data, as well as by testing functional capacity and performance. Further indicators for wellness can be obtained from demographic, socioeconomic and epidemiological data, which can be used to appraise access to food, shelter, education, employment, healthcare and consumer goods, as well as to rate health risks, ecological footprint, morbidity, mortality and life expectancy (Cohen 2008a).

The multidimensional nature of wellness makes any single measure inadequate, and so attempts have been made to combine measures from the different domains. For example, the BankWest Quality of Life Index tracks Australian living standards across municipalities based on key indicators of the labour market, the housing market, the environment, education and health (BankWest 2008).

In attempting to measure 'full spectrum wellness', Travis and Ryan adopt the concept of a 'wellness energy system', which implies a thermodynamic model and measures wellness in terms of inputs and outputs. They acknowledge that 'we are all energy transformers, connected with the whole universe', and that 'all our life processes, including illness, depend on how we manage energy' (Travis & Ryan 2004). These authors further describe 12 aspects of wellness, which include inputs provided by breathing, eating, and sensing, and outputs described as self-responsibility and love, transcending, finding meaning, intimacy, communicating, playing and working, thinking, feeling and moving. These 12 aspects of wellness are the basis for the wellness inventory: evolved from health-risk appraisal techniques to become the first computerised wellness assessment tool, this inventory aims to provide a measure of wellness across the 12 dimensions through a self-reported questionnaire.

Perhaps the most comprehensive attempt to create a metric for wellbeing is the 'Happy Planet Index', which uses both subjective and objective data in an attempt to measure the ecological efficiency with which countries achieve long and happy lives for their citizens. The Happy Planet Index is a composite measure that is calculated by multiplying life satisfaction by life expectancy and then dividing by ecological footprint. It therefore takes a thermodynamic approach to the wellness of populations by dividing outputs (the length and happiness of human life) by inputs (natural resources) (Marks et al 2009). The finding that the average scores across nations are low, that all nations could do better and that no country does well on all three indicators or achieves an overall high score on the index has led the Happy Planet Index to be considered currently as the (Un)Happy Planet Index (Marks et al 2009).

THE WELLNESS REVOLUTION

Since the emergence of self-reflective consciousness, every culture at every point in history has maintained various practices that aim at achieving and maintaining the wellbeing of individuals and the wider community. These practices invariably include the use of the local environment, food, water and plants, as well as various indigenous healing practices, such as massage and traditional cultural practices that are performed to focus the mind and anchor the experience of being well in ritual, routine and direct sensual experience.

While every culture throughout history has had its own wellness practices and philosophies, a culture that is global or sustainable has never existed before (Cohen 2008a). In the current millennium, however, there is a need for global solutions that provide an integrated response to the many world crises and an orientation towards wellness promises to provide such solutions. Thus it is suggested that along with the current crises, the world is also experiencing the start of a 'wellness revolution' and the accompanying growth of a 'wellness industry'.

THE WELLNESS INDUSTRY

In his 2002 book *The wellness revolution*, economist Paul Zane Pilzer estimated that the value of existing items in the US wellness industry had reached approximately US$200 billion. This included US$70 billion for vitamins and US$25 billion for spas and fitness centres — about half the amount spent on automobiles in the USA (Pilzer 2002). Pilzer suggests that the US$200 billion is only the tip of the iceberg, and that wellness products and services represent the beginning of a new trillion-dollar sector of the US economy. In an updated edition of his book, Pilzer estimates that in 2007 the US wellness industry had expanded to over US$500 billion and that the untapped market for wellness had increased in size thanks to millions of new wellness consumers (Pilzer 2007).

The growth of the wellness industry is evidenced by the dramatic growth of the global spa industry (now considered by many to be the 'spa and wellness' industry), which has recently

emerged as a global phenomenon through a convergence of industries, traditions and therapeutic practices. While spa therapies have been around since ancient times in many different forms that reflect the cultural, social and political milieu in which they are embedded, these practices are now being rediscovered, integrated and branded to create a new global industry that draws from a range of aligned industries, including beauty, massage, hospitality, tourism, architecture, property development, landscape design, fashion, food and beverage, fitness and leisure, personal development, as well as complementary, conventional and traditional medicine (Cohen 2008a).

Fuelled by the merging of the travel dollar with the health dollar, spas are now springing up all over the world and have become a standard feature of luxury hotels and resorts. Spas are reported to be the fastest-growing leisure industry, and it is estimated that by 2001 revenues from spas had already overtaken revenues from amusement parks, box office receipts, vacation ownership and ski resorts (ISPA 2002). A more recent report on the global spa economy suggests that global revenue from spas in 2007 was worth more than US$255 billion globally and that the wider wellness industry was worth an additional US$1.1 trillion (SRI International 2008).

In offering to deliver on wellness, the spa industry is moving beyond luxury and pampering into the area of providing healthcare and, even further, raising consciousness. As such, the global spa industry is a melting pot for a whole host of products and services that encourage enhanced health and wellbeing and are drawn from a wide variety of traditions that include conventional, complementary and traditional medicine. Thus spas are adopting an integrative approach; they are taking holistic medical concepts out of clinics and combining them with the world of hospitality and leisure to place them in sustainable, enjoyable and nurturing environments.

Hotels certainly have a much greater appeal than hospitals. By combining hospitality with an integrative medicine model that emphasises lifestyle change and personal empowerment, the spa and wellness industry has the potential to transcend conventional medicine and create a globally sustainable health system. While most spas do not, as yet, create formal medical records, instigate diagnostic tests or perform medical procedures, these are all taking place in some medi-spas and destination spas, while some spas are beginning to integrate conventional and complementary medicine services with hospitality services such as accommodation, food and beverage to create hybrid hospital-spa-hotels ('hos-spa-tels'). As these are integrated into international hospitality chains, they create the potential for the delivery of a global integrated health service based on wellness principles (Cohen 2008a).

CONSCIOUS CONSUMPTION

The rise of the wellness industry is aligned with a move towards 'lifestyles of health and sustainability' (LOHAS). LOHAS is a demographic defining a particular market segment related to sustainable living and 'green' ecological initiatives, and is generally composed of a relatively upscale and well-educated population segment. In 2006 the LOHAS market segment was estimated at approximately US$209 billion for goods and services focused on health, the environment, personal development and sustainable living. The focus of LOHAS is conscious consumption and covers diverse market segments such as personal health, natural lifestyles, green building, alternative energy and transportation, and ecotourism (for more information about LOHAS, see www.lohas.com).

A strong component of the LOHAS movement is the trend for consumers to choose more holistic, prevention-based models of healthcare, and this is evidenced by the increasing use of complementary and alternative medicine (Tindle et al 2005). This trend may reflect a growing disenchantment with the medical profession's seemingly one-sided emphasis on science and technology, as well as a growing demand for autonomy in healthcare decisions. Certainly, the general population is now better informed than ever and has better access to health information. The public are subsequently demanding more from healthcare providers and are not interested only in treating illness. Instead they want to maximise their health, prevent or slow down the ageing process and achieve higher levels of functioning (Cohen 2001).

The LOHAS movement has arisen out of a growing awareness that rampant consumerism seems to be taking over and destroying the planet. Certainly, unchecked and unconscious consumption can be seen to be at the root of many of the world's problems. Thus while we as consumers currently have access to a seemingly unlimited choice of goods in every size

and colour, we remain disconnected from the products and services we purchase and often do not know where they come from, how they are produced, who produced them, what is in them, how they are disposed of or who benefits from their purchase.

In response to this, there is a growth in conscious consumer trends that include LOHAS, as well as a variety of trends badged with different labels such as; 'green', 'natural', 'organic', 'fair-trade', 'corporate social responsibility', 'eco', 'ethical investment', 'sustainable', 'barefoot luxury'. These have given rise to 'locovor' restaurants (those that source food within 160 kilometres/100 miles), carbon offset programs, green buildings, 'carbon neutral businesses', 'ecotourism', 'ethnotourism', 'voluntourism', 'downsizing', 'compacting', 'tree-change', 'social capital' and 'triple and quadruple bottom-line reporting'.

It is suggested that this range of conscious consumer trends can be integrated under the banner of 'conshumanism', which is a term that defines 'conscious and humane consumption' or 'consumption with maximal awareness, efficiency and enjoyment and minimal pain, energy, waste and pollution' (Cohen 2008a). Conshumanism embraces an overarching concept that can integrate multiple consumer trends towards greater transparency, equity, accountability, social responsibility, environmental sustainability and ethics. The common feature of these trends is increasing information and consciousness about consumption as well as incorporating an awareness of wellness into everyday lifestyle decisions.

TOWARDS A WELLNESS POLICY AGENDA

While treating illness has traditionally been the domain of the medical system, there is a growing realisation that wellness is holistic and multifaceted, and that implementing a wellness agenda requires wellness to become part of the fabric of our society so that it infiltrates the education system, workplaces and the consciousness of every individual. Thus action is required from all sectors, from individuals, government and non-government agencies to the corporate sector.

GOVERNMENT INITIATIVES

The year 2008 seems to have been a watershed year for Australian government wellness initiatives. The Australia 2020 Summit called for the development of a 'whole-of-life wellness model' and a 'wellness footprint' to evaluate, measure and resource services across portfolios (Good & Roxon 2008), while the National Health and Hospitals Reform Commission, the National Preventative Health Task Force, the Primary Health Care Strategy Reference Group and the Indigenous Health Equity Council were established, all with a mandate for health reform (Moodie et al 2008).

Established in February 2008, the National Health and Hospitals Reform Commission (NHHRC) came out with a set of guiding principles that include 'strengthening prevention and wellness', and acknowledged that a comprehensive and holistic approach is needed to reorient the health system, so that there is greater emphasis on helping people stay healthy through stronger investment in wellness, prevention and early detection and appropriate intervention to maintain people in as optimal health as possible (NHHRC 2008). In October 2008 the NHHRC commissioned an options paper on 'A national agency for promoting health and preventing illness' (Moodie et al 2008), which proposes the establishment of a National Health Promotion and Prevention Agency in order to provide education, evidence and research to make prevention a top priority. This options paper was followed by the publication of an interim report, *A healthier future for all Australians*, a major theme of which was 'Taking responsibility', calling for greater personal responsibility for improving health supported by policies that make healthy choices easier; health literacy in a national curriculum for all schools; better information about creating healthy local communities — 'wellness footprints'; and workplace health promotion and wellness programs (Bennett 2008).

In line with these developments, the National Preventative Health Taskforce was established in April 2008 to provide evidence-based advice to governments and health providers on preventative health programs and strategies, focusing on the burden of chronic disease currently caused by unhealthy lifestyles. This taskforce produced a discussion paper entitled 'Australia, the healthiest country by 2020', which acknowledges the need for a coordinated approach to wellness, stating that:

> Our health is not only determined by our physical and psychological make-up and health behaviours, but also by our education, income and employment; our access to services; the place in which we live in [sic] and

its culture; the advertising we are exposed to; and the laws and other regulations in place in our society (Preventative Health Task Force 2008).

WORKING TOWARDS WELLNESS

In addition to the above initiatives taken by the Australian government, 2008 saw a number of global initiatives with a call for a more proactive, wellness-oriented approach to be taken by the corporate sector. Illness places a huge burden not only on government health systems and communities, but also on industry, with the potential for catastrophic effects. While the costs to industry from illness due to absenteeism are clear, it is only recently that the costs of 'presenteeism' have been assessed. It has been estimated that presenteeism — when workers turn up for work but are unproductive because of an ongoing illness — involves a greater cost than absenteeism, and may represent up to 60% of an employee's total lost productivity and medical costs (Goetzel et al 2004). Presenteeism may also pose serious threats to workplace safety, lead to dissemination of infectious diseases and have hidden long-term costs as well as compounding other lifestyle and social issues.

There is therefore a clear advantage in addressing wellness in the workplace, as this may have a positive impact on a company's productivity, recruitment, retention and ultimate profitability. As many employees spend a significant portion of their life at work, workplace wellness programs are also well positioned to address the growing burden of chronic lifestyle-related disease.

At the World Economic Forum Annual Meeting in Davos, Switzerland, in January 2008, there was a call for action to raise the issue of employee health on the corporate agenda. At the meeting, the results of a collaboration between the World Economic Forum and the World Health Organization were released that suggested that workplace wellness programs are a real, but underexploited, opportunity to tackle the growing worldwide epidemic of chronic disease. This coincided with a PriceWaterhouseCoopers report entitled *Working towards wellness: accelerating the prevention of chronic disease*, which suggests that large multinational corporations are now looking for wellness strategies to implement in their workplaces and the communities in which they operate, and are rolling out comprehensive wellness programs in multiple countries, even though there are challenges in the implementation, evaluation and monitoring of such programs (PriceWaterhouseCoopers 2007).

As yet there is still no robust accounting for wellness, despite the evolution of triple and quadruple bottom-line reporting; however, the corporate sector appears to be taking workplace wellness programs beyond health screening and occupational health and safety programs, and there are moves to engage employees and the wider community in wellness and lifestyle initiatives through corporate social responsibility, environmental sustainability and community development agendas.

LIFESTYLE MEDICINE

Wellness impacts on every aspect of our lives, and experiencing wellness requires the holistic integration of multiple factors that determine physical, psychological, emotional, social, economic, environmental and spiritual health. Wellness is therefore ultimately an issue of lifestyle. In order to embrace wellness or enhanced health, the key 'life activities' that determine our health must be addressed. These life activities are summarised by the SENSE approach (see Ch 1). We all need to manage stress, move, eat, interact with other people, interact with the world, and learn. If we improve the way we do these activities, we will naturally improve our wellbeing. Wellness therefore involves the following:

- **stress management** — managing stressors (e.g. effective time management strategies and priority setting), and including everyday activities that enhance our ability to cope with stressors (e.g. meditation, breathing exercises, hobbies, and infusing life with creativity, humour and fun)
- **exercise** — engaging in regular physical activity that improves our aerobic capacity (e.g. walking), physical strength (e.g. resistance training) and flexibility (e.g. yoga)
- **nutrition** — receiving adequate nutrition through the consumption of a wide variety of fresh, seasonal, whole foods that are stored and prepared appropriately; minimising our exposure to toxins by using organic produce; and avoiding tobacco smoke and environmental toxins
- **social and spiritual interaction** — devoting ourselves to quality time with others and fostering love and intimacy in all our personal relationships; developing an ethic of service to others and a sense of

social responsibility (e.g. volunteering and community work); giving to charities (e.g. time, effort, money); ethical investing and purchasing

- **education** — learning about ourselves and others, our environment and our place in it, and attempting to avoid obvious hazards while living sustainable, ecological lifestyles.

In recognition of the impact that lifestyle has on illness, developments in health funding in Australia have enabled allied health professionals to become part of a team that can address lifestyle issues. This has led to the emergence of 'lifestyle medicine', which is deemed to be a new discipline that attempts to bridge the gap between health promotion and conventional medicine by applying 'environmental, behavioural, medical and motivational principles to the management of lifestyle related health problems in a clinical setting' (Egger et al 2008).

Managing lifestyle issues changes the emphasis from conventional treatment to one where patients need to be more involved in their own care, and which therefore requires the clinician to have considerable motivational knowledge and skills. It involves the therapeutic use of lifestyle interventions in the management of disease (Egger et al 2009). Lifestyle medicine may also involve health coaching, which is a practice in which health professionals apply evidence-based psychological, counselling and coaching principles and techniques to assist their patients to achieve positive health and lifestyle outcomes through cognitive and behaviour change (Gale 2009).

A NEW ACADEMIC DISCIPLINE

It appears that the wellness revolution has created the opportunity for wellness to be framed as a new academic discipline. The multidimensional and holistic nature of wellness, however, demands extensive collaboration and communication across diverse discipline areas of expertise to work on wellness-oriented teaching, learning and research projects.

Wellness seems to have an emerging research agenda, with one of the four Australian Government National Research Priorities being 'Promoting and maintaining good health'. This priority area aims to support preventative healthcare and enable people to make healthy choices, and includes the following key research themes: a healthy start to life, ageing well, ageing productively and preventive healthcare (Department of Education, Employment and Workplace Relations 2009). While this research priority area seems to target wellness-related research, wellness underpins many disparate research areas, ranging from theoretical and bench-top science to clinical research as well as social and policy research. A wellness agenda is therefore also inherent in other research priority areas, such as sustainability, frontier technologies and safeguarding Australia from terrorism, crime, invasive diseases and pests.

While a wellness research agenda is emerging, significant hurdles remain. Specific research into wellness and disease prevention is hindered by a lack of discrete outcome measures with which to measure wellness. Additional challenges include the design of programs that monitor and promote adherence, novel delivery models and the training, regulation and accreditation of suitable practitioners.

Although training and regulation pose challenges, wellness is a growing area in education and training and is increasingly becoming the focus of academic programs at undergraduate and postgraduate levels. International demand for a wellness-oriented academic program is located in three principal healthcare sectors: the conventional healthcare disciplines, which have an increasing emphasis on health promotion; the complementary and allied health sector including fitness, sports science, nutrition and psychology; and the rapidly growing hospitality, leisure and spa sector.

The need for wellness-related education is demonstrated by current health workforce shortages, the lack of experienced managers and therapists to work in spas, hospitality and leisure and the need for business professionals to embrace workplace wellness. A Productivity Commission report on Australia's health workforce suggested four broad approaches to overcome current health workforce shortages and distribution problems, and to address the future pressures facing the system. The first of these approaches involves strategies aimed at reducing the underlying demand for healthcare through 'wellness' and preventative strategies. This report also commented on the need for a health workforce with increased skills in health promotion (Productivity Commission 2006).

Creating a new academic discipline around wellness is a challenge, as there is a need to align the wellness industry with the professional and educational standards of the healthcare and business sectors. Such an alignment is evident in the continual increase in the

provision and standard of education programs in wellness-related areas such as naturopathy, massage, fitness, yoga and spa therapies. This has led to calls for wellness-education-related accreditation and standards. In answering this call, the US National Wellness Institute recently set up an Academic Accreditation Committee and developed a set of baccalaureate-degree-level standards and processes that will lead to accreditation of academic programs and graduate certification (US National Wellness Institute 2008).

In Australia, RMIT University has taken on a leadership role and established the world's first postgraduate Master of Wellness program (see www.rmit.edu.au/healthsciences/wellness). While no position descriptions currently require applicants to have a postgraduate wellness degree, this program provides core subjects and a suite of electives that include healthcare- and business-related courses so that students can choose their own path, build on their existing skills and become equipped to lead the wellness revolution in their respective disciplines. Thus the program is designed to provide graduate students from diverse backgrounds, including both health science and business graduates, with a holistic overview of wellness principles and practices. The program also aims to have a positive impact on students' personal health and wellbeing, and uses cutting-edge educational technology and the latest understanding about adult teaching and learning to deliver a fully online program with a global reach.

WELLNESS ONLINE

Wellness is a product of consciousness and it is said that 'the currency of wellness is connection' (Travis & Ryan 2004). With the advent of the internet as well as the development of information and communications technology (ICT), the world is certainly becoming more connected. Over the past two decades the development of the internet and ICT has progressed so rapidly that it is now possible for everyone on the globe to be linked via mobile communications technology that infiltrates almost every aspect of society.

It is clear that wellness-related technologies are converging in an online environment. Already ICT is used to support healthcare delivery, and electronic health-information systems promise to improve efficacy, safety and quality of care through the provision of alerts and reminders, diagnostic support, therapy critiquing and planning, prescribing decision support, information retrieval, image recognition and interpretation, as well as through the discovery of new phenomena and the creation of medical knowledge (Coiera 2003).

The advent of personal computing and modern consumer electronics has made technologies that were once accessible only to technical specialists available to the general population via home-based and mobile platforms. For example, online calculators can provide the basis for lifestyle advice and motivation for implementing positive lifestyle changes, and online tools can provide assessments via subjective questionnaires as well as by the direct testing of cognitive and other functional status.

Biometric monitors allow remote wellness monitoring by uploading data on various physiological parameters such as activity and sleep. These devices are being integrated into other personal electronic devices such as phones and digital music players. For example, Apple and Nike offer a kit in which a shoe sensor communicates with a wireless iPod receiver to transmit workout information such as elapsed time, distance travelled, and calories burned (see www.apple.com/ipod/nike) (Cohen 2008b).

Online data collection allows personal information to be analysed and interpreted with the assistance of online experts, who in turn have access to sophisticated knowledge-management technologies, including bibliographic databases and decision support systems. Furthermore, online education offers unprecedented opportunities to deliver education across the planet, and develop knowledge and skills wherever they are required.

THE FUTURE OF WELLNESS

While the worldwide web is only around 5000 days old, when considered as a single machine it represents the largest and most reliable machine ever built with information-processing power approaching the same order as a human brain. The size and power of the web is doubling every two years, and it is expected that its future evolution will lead to services and opportunities that are yet to be imagined (Kelly 2007). Its global reach provides a unique platform for connecting people, ideas and practices, essential parts of the wellness equation. How best to harness its capabilities to improve individual and global wellness is still unclear. Will initiatives such as Google

Health be able to provide everyone on the planet with a free online health record and provide continuity of care as well as opportunities for epidemiological research and public health initiatives? Will online access provide everyone with access to education and the wealth of the world's knowledge? Will 'augmented reality' become the norm and 'virtual reality' become indistinguishable from 'reality'? Will video games become better than real life? Will social networking provide a forum for meaningful connection and provide an end to loneliness and social isolation? Will online environments facilitate therapeutic and health enhancing experiences? Will the harnessing of global connectivity be able to enhance how we experience our environment and avert the many crises we are facing?

It seems clear that over the next few decades changing global demographics, accompanied by major societal changes brought about by climate change, and technological innovations will have an impact on personal, community and global wellbeing and will for ever change how humans live. The development of wellness as a key focus for research, education, healthcare, government policy and industry can only improve the outlook for present and future generations.

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Adhatoda

HISTORICAL NOTE An important herb in Ayurvedic medicine for hundreds of years, adhatoda is used traditionally for cough, asthma, bronchitis and tuberculosis. Its common name, 'vasa', means perfume; it is an evergreen perennial shrub that grows all over the plains of India and Sri Lanka (Pole 2006).

COMMON NAMES
Adhatoda, Malabar nut tree

OTHER NAMES
Adhatoda zeylanica, arusha, bakash, Justicia adhatoda-Folium, vasaka, vasa, adusa, Baga-bahouk

BOTANICAL NAME/FAMILY
Adhatoda vasica (family Acanthaceae)

PLANT PARTS USED
Leaves and roots

CHEMICAL COMPONENTS
The leaves contain several different alkaloids, including vasicine, vasicinone, vasicinol, adhatodine, adhatonine, adhavasinone, anisotine, peganine, 7-methoxyvaicinone, desmethoxyaniflorine, 3-hydroxyanisotine, vasnetine (Claeson et al 2000, Mhaske & Argade 2006, Kamal et al 2006), betaine, steroids and alkanes. The root also contains alkaloids (vasicinol, vasicinolone, vasicinone, adhatonine), a steroid (daucosterol), carbohydrates and alkanes (Claeson et al 2000).

MAIN ACTIONS
Indigenous usage in India and Sri Lanka was as an antispasmodic, antiseptic, insecticide and antidote to fish poisoning. Current application focuses on the herb's antispasmodic, oxytocic and cough-suppressant activities (Gurib-Fakim 2006). It is an ingredient in the Rasayana preparation called chyavanprash, which is used widely as a health-promotive and disease-preventative tonic and is believed to be hepatoprotective and immunomodulating (Govindarajan et al 2007).

As with many Ayurvedic herbs, most investigation has been undertaken in India and locating original research from these sources is difficult.

Antitussive effects
Results from animal studies show that *Adhatoda vasica* extract exerts considerable antitussive activity when administered orally and is comparable to codeine when cough is due to irritant stimuli (Dhuley 1999). The antitussive activity may be due to the action of vasicinone and vasicinol, which have activity in the cerebral medulla. In Ayurvedic medicine, adhatoda is prescribed in combination with *Curcuma longa*, *Zingiber officinale*, *Glycyrrhiza glabra*, *Terminalia chebula*, *Ocimum sanctum* and *A. vasica* to control cough and shortness of breath, especially for lung cancer patients (Nayak 2002).

> ***Clinical note***
> One of the alkaloids found in the herb (vasicine) has been chemically modified and is referred to as RLX (6,7,8,9,10,12-hexahydroazepino-[2,1-b]-quinazoline-12-one) in the medical literature (Johri & Zutshi 2000). It has been shown in animal studies to inhibit antigen-induced mast-cell degranulation and histamine release and to exert bronchodilator activity. It is the lead molecule for Bromhexin and Ambroxol (Gurib-Fakim 2006).

Anti-inflammatory
Potent anti-inflammatory activity has also been demonstrated for the alkaloid fraction deoxyvasicinone (22), the naturally occurring quinazolinone alkaloid (Mhaske & Argade 2006). This has been shown to be equivalent to the anti-inflammatory effect of hydrocortisone in one study (Chakraborty & Brantner 2001).

Bronchodilator and anti-asthmatic activity
According to a 2002 review, both vasicine and vasicinone possess in vitro and in vivo bronchodilatory activity and inhibit allergen-induced bronchial obstruction in a manner comparable to that of sodium cromoglycate (Dorsch & Wagner 1991, Jindal et al 2002).

OTHER ACTIONS

Hepatoprotective
A. vasica leaf (50–100 mg/kg) was shown to protect against induced liver damage in rats (Bhattacharyya et al 2005); 100 mg/kg of *A. vasica* was comparable to the hepatoprotective ability of silymarin at 25 mg/kg. An earlier study showed that *A. vasica* (100–200 mg/kg) protected against carbon tetrachloride-induced liver damage in rats (Pandit et al 2004). The leaf extract significantly enhanced the protective enzymes superoxide dismutase and catalase in the liver: 200 mg/kg of

A. vasica was shown to be comparable to 25 mg/kg of silymarin. Traditionally adhatoda was used to treat liver disease—the juice of fresh leaves (5–10 g) was mixed with honey and orally ingested three times daily for 2–3 weeks (Kotoky & Das 2008).

Protection against radiation damage

Adhatoda vasica (800 mg/kg) protects hematopoietic stem cells against radiation damage by inhibiting glutathione (GSH) deletion, reducing lipid peroxidation and increasing phosphatase activity in mice (Kumar et al 2005). Animals pretreated with oral doses of adhatoda showed an 81.25% survival rate at 30 days as compared to control animals, who could not survive past 25 days. In additional studies on mice, adhatoda exhibited highly significant increases in GSH content and significant decrease in lipid peroxidation (Samarth et al 2008).

Enzyme induction

In vitro tests show that *A. vasica* acts as a bifunctional inducer, since it induces both phase I and phase II enzyme systems (Singh et al 2000). The clinical significance of this finding is unclear and remains to be tested.

Abortifacient

One of the traditional uses of the herb is as an abortifacient; however, inconsistent results from in vivo studies have made it difficult to determine whether adhatoda has significant abortifacient activity. One animal study investigating oral administration of leaf extracts showed 100% abortive rates at doses equivalent to 175 mg/kg of starting dry material (Nath et al 1992). Another study found that an *A. vasica* extract had anti-implantation activity in 60–70% of test animals (Prakash et al 1985).

Antispasmodic

The essential oil from the leaves exerts antispasmodic action, as demonstrated in an animal model of guinea pig tracheal chain (Claeson et al 2000).

Antioxidant activity

In vitro tests on mice also show the extract is effective in inducing glutathione S-transferase and DT-diaphorase in lungs and forestomach, and superoxide dismutase and catalase in kidneys (Singh et al 2000).

Nematocidal/anticestodal activity

In rat studies, Naga tribes in India have traditionally used adhatoda for curing intestinal worm infestations. Animal studies indicate that crude aqueous root extracts of 3 g/kg body weight exhibit 37.4% reduction of mixed gastrointestinal nematode infestations in sheep, as a result of the alkaloid and glycoside content of adhatoda (Lateef et al 2003, Githiori et al 2006). In one animal study, adhatoda exhibited significant anticestodal efficacy, greater than that of praziquantel (Yadav et al 2008).

Other

Deoxyvasicinone (22), the naturally occurring quinazolinone alkaloid, exhibits antimicrobial and antidepressant activities (Mhaske & Argade 2006). Antimicrobial activity was specific to certain strains of penicillin- and ciprofloxacin-resistant *Neisseria gonorrhoea* (Shokeen et al 2009).

CLINICAL USE

Adhatoda has not been significantly investigated in clinical studies, so information is generally derived from in vitro and animal studies and is largely speculative.

Cough

The antitussive activity of adhatoda extract has been compared to that of codeine in two different models of coughing and in two different animal species (Dhuley 1999). When administered orally, *A. vasica* extract produced antitussive effects comparable to those of codeine against coughing induced by peripheral irritant stimuli. When coughing was induced by electrical stimulation of the tracheal mucosa, adhatoda extract was only one-quarter as active as codeine. Intravenous administration was far less effective in both cough models. A double-blind, randomised, controlled trial of *Adhatoda vasica* in combination with *Echinacea purpurea* and *Eleutherococcus senticosus* was compared with an *Echinacea* and *Eleutherococcus* mixture and bromhexine (Narimanian et al 2005). Bromhexine is a semi-synthetic derivative of the alkaloid vasicine found in *A. vasica* (Grange & Snell 1996) and is found in some pharmaceutical cough mixtures. Compared with the other two formulas, the *A. vasica* combination reduced the severity of cough, increased mucus discharge and reduced nasal congestion. Both herbal mixtures reduced the frequency of cough compared with bromhexine. Furthermore, Grange and Snell (1996) identified pH-dependent growth inhibitory effects on *Mycobacterium tuberculosis*, which further supports its usage as a mucolytic.

Asthma

Although *A. vasica* is used for asthma in combination with other herbs, clinical evidence is limited. Evidence of bronchodilator activity from in vitro and animal studies provides a theoretical basis for use in treating asthma.

One 12-week randomised, double-blind, placebo-controlled clinical trial was undertaken to assess the efficacy of an Ayurvedic herbal formula in asthmatic patients. While the formula contained 15 different herbs, almost half the total weight consisted of adhatoda. Active herbal treatment increased the efficacy of medication (salbutamol and theophylline) in bronchodilation, thus increasing forced expiratory volume in the first second (FEV_1). In addition, the herbal combination significantly improved other clinical parameters, resulting in reductions in dyspnoea, wheezing, expectoration, disability and respiratory rate when compared to a placebo (Murali et al 2006). Although these results are promising, the role of adhatoda as a stand-alone treatment remains unclear.

OTHER USES

Adhatoda is traditionally used to treat cough, asthma, bronchitis and colds, but has also been used to treat fever, dysentery, diarrhoea, jaundice,

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PRACTICE POINTS/PATIENT COUNSELLING

- Adhatoda is an important Ayurvedic medicine used in the treatment of cough, asthma, bronchitis and colds.
- Traditional use further includes fever, dysentery, diarrhoea, jaundice, tuberculosis and headache.
- Preliminary evidence suggests that adhatoda may have bronchodilator activity and inhibit allergen-induced bronchoconstriction; however, clinical studies are unavailable to determine clinical significance.
- Antitussive effects comparable to those of codeine have also been reported in animal studies in which cough has been peripherally induced.
- Adhatoda has been used to stimulate the birthing process and aid healing afterwards, and may have abortifacient activity.
- Overall, little clinical evidence is available. Much of the available information is therefore speculative and based on in vitro and animal research and traditional use.

tuberculosis and headache, to stimulate the birthing process and aid healing afterwards, and as an antispasmodic (Claeson et al 2000). It has also been used as an abortifacient in some Indian villages.

Leaves that have been warmed on the fire are applied topically in the treatment of joint pain, lumbar pain and sprains.

Use of the powder is reported as a poultice on rheumatic joints, a counterirritant for inflammatory swelling, a treatment for fresh wounds, and in urticaria and neuralgia (Dhuley 1999).

DOSAGE RANGE

As clinical research is lacking, the following dosages come from Australian manufacturers' recommendations.

- Liquid extract tincture (1:2): 1–3 mL/day (Pole 2006).
- Liquid extract tincture (1:5): 2.5–7.5 mL/day (Pole 2006).
- Dried herb/powdered leaf: 0.5–1.5 g/day (Pole 2006).

ADVERSE REACTIONS

Insufficient reliable information is available.

SIGNIFICANT INTERACTIONS

Controlled studies are not available, so interactions are based on evidence of activity and are largely theoretical and speculative.

Codeine and other antitussive drugs

Theoretically, adhatoda may increase the antitussive effects of these drugs—beneficial interaction may be possible under professional supervision.

CONTRAINDICATIONS AND PRECAUTIONS

Insufficient reliable information is available.

PREGNANCY USE

Adhatoda is contraindicated in pregnancy, as the herb may have abortifacient activity. In Ayurvedic medicine it is considered safe post-partum (Pole 2006), and is used in combination with *Bacopa monnieri* and 12 other herbal medicines in the treatment of vaginal discharge, pregnancy pain and pregnancy fever (Jadhav & Bhutani 2005).

PATIENTS' FAQs

What will this herb do for me?

Because adhatoda has been investigated mainly in animal and test-tube studies, its effects on humans are uncertain. Based on preliminary information and historical use, it may suppress cough and have some beneficial effects in asthma.

When will it start to work?

This is uncertain because insufficient research data are available.

Are there any safety issues?

Some research suggests that adhatoda may stimulate uterine contractions, so it is not recommended in pregnancy.

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Albizia

HISTORICAL NOTE It is believed that albizia received its name because Filipo del Albizi, an 18th century Florentine nobleman, introduced the species into cultivation (The Plants Database 2004). It has been used in Ayurvedic medicine for many years and is still a popular treatment for asthma, allergy and eczema.

COMMON NAME
Albizia

OTHER NAMES
Pit shirish shirisha

BOTANICAL NAME/FAMILY
Albizia lebbeck (family Fabaceae)

PLANT PARTS USED
Leaves and stem bark

CHEMICAL COMPONENTS
These are poorly understood, but albizia has been reported to contain albiziasaponins A, B and C, epicatechin, procyanidins and stigmastadienone.

MAIN ACTIONS
Albizia has not been significantly investigated in clinical studies; therefore, information is generally derived from in vitro and animal studies and is largely speculative.

Stabilising mast cells
Both in vitro and in vivo tests have reported significant mast-cell-stabilisation effects similar to those of cromoglycate (Johri et al 1985, Tripathi et al 1979). One study found that degranulation was inhibited by 62% (Tripathi et al 1979). The saponin fraction is believed to be the key group responsible for activity. A more recent in vitro study compared the effects of albizia leaf, albizia stem bark and disodium chromoglycate on mast-cell stabilisation. All three compounds were found to be equally potent (Shashidhara et al 2008).

Altering neurotransmitter activity
Albizia has an influence on GABA, serotonin and dopamine levels, according to in vivo studies (Chintawar et al 2002, Kasture et al 2000). It appears that different fractions within the herb exert slightly different effects on neurotransmitters. In one study, a saponin-containing fraction from the extract of dried leaves of albizia was shown to decrease brain concentrations of GABA and dopamine, whereas serotonin levels increased. Another study that tested the methanolic fraction of an ethanolic extract of albizia leaves found that it raised brain levels of GABA and serotonin (Kasture et al 2000). Additionally, anticonvulsant activity has been demonstrated in vivo for this fraction.

Memory enhancement
Saponins isolated from albizia have been shown to significantly improve the memory retention ability of normal and amnesic mice, compared with their respective controls (Une et al 2001).

Reduces male fertility
Three studies using animal models have demonstrated that albizia significantly reduces fertility in males (Gupta et al 2004, 2005, 2006).

Albizia saponins A, B and C (50 mg/kg) isolated from the stem bark have been shown to significantly reduce the weight of the testis, epididymides, seminal vesicle and ventral prostate of male rats (Gupta et al 2005). A significant reduction in sperm concentration was also noted and albizia reduced fertility by 100% after 60 days. A follow-up study administered oral doses of methanolic bark extract (100 mg/day) for 60 days (Gupta et al 2006). Testis, epididymides, seminal vesicle and ventral prostate weights along with sperm motility and density

were all significantly decreased compared to controls, also resulting in a 100% drop in male fertility. The methanolic extract of albizia pods (50, 100 and 200 mg/kg) was also shown to significantly decrease fertility and arrest spermatogenesis in rats after 60 days (Gupta et al 2004).

OTHER ACTIONS

Other actions seen in vitro and in vivo include antioxidant, antifungal and antibacterial actions, antispasmodic effect on smooth muscle, positive inotropy and an immunostimulant effect (Barua 2000, Bone 2001, Kasture et al 2000, Resmi et al 2006). Cholesterol-lowering activity has been demonstrated in vivo (Tripathi et al 1979).

CLINICAL USE

Albizia has not been significantly investigated under clinical trial conditions, so evidence is derived from tradition, in vitro and animal studies.

Allergy and asthma

Albizia is mainly used to treat allergic rhinitis, urticaria and asthma in clinical practice. In vitro and in vivo evidence of mast-cell stabilisation provide a theoretical basis for its use in allergic conditions; however, the clinical significance is unknown.

OTHER USES

Traditionally, a juice made from the leaves has been used internally to treat night blindness. The bark and seeds have been used to relieve diarrhoea, dysentery and treat haemorrhoids, most likely because of their astringent activity. The flowers have been used as an emollient to soothe eruptions, swellings, boils and carbuncles. In Ayurvedic medicine, it is used to treat bronchitis, asthma, allergy and inflammation.

DOSAGE RANGE

As clinical research is lacking, the following dosages come from Australian manufacturer recommendations.

- Liquid extract (1:2): 3.5–8.5 mL/day or 25–60 mL/week.
- Dried herb: 3–6 g/day.

TOXICITY

This is unknown; however, research with the methanolic fraction of albizia extract has identified a median lethal dose of 150 mg/kg (Kasture et al 2000).

ADVERSE REACTIONS

Insufficient reliable information available.

SIGNIFICANT INTERACTIONS

Controlled studies are not available; therefore, interactions are based on evidence of activity and are largely theoretical and speculative.

Barbiturates

Additive effects are theoretically possible, as potentiation of pentobarbitone-induced sleep has been observed in vivo — use with caution.

Antihistamines and mast-cell-stabilising drugs

Additive effects are theoretically possible because both in vitro and in vivo tests have identified significant mast-cell-stabilisation activity similar to that of cromoglycate — potentially beneficial interaction.

Tricyclic and selective serotonin reuptake inhibitor antidepressant drugs

Increased risk of serotonin syndrome is theoretically possible, as albizia increases serotonin levels, according to in vivo studies — observe patient.

CONTRAINDICATIONS AND PRECAUTIONS

Significant reductions in male fertility have been reported in tests using animal models; however, it is not known whether the effects also occur in humans. Until further research is conducted, caution is advised.

PREGNANCY USE

Insufficient reliable information available. Based on animal studies indicating a significant effect on male fertility, males with low sperm counts or poor sperm motility should avoid this herb if attempting to father a child.

PRACTICE POINTS/PATIENT COUNSELLING

- Albizia is a traditional Ayurvedic herb used to treat allergies, asthma, eczema and inflammation.
- Preliminary research has shown that it has significant mast-cell-stabilisation activity comparable to cromoglycate, and has also identified memory enhancement activity and possible anticonvulsant effects.
- Overall, little clinical evidence is available; therefore, much information is speculative and based on in vitro and animal research.

PATIENTS' FAQs

What will this herb do for me?

Albizia is a traditional Ayurvedic medicine used to reduce allergic conditions, such as allergic rhinitis and urticaria. It is also used for atopic conditions, such as eczema and asthma, when indicated. Controlled trials have not been conducted, so it is uncertain whether it is effective.

When will it start to work?

This is uncertain because insufficient research data are available.

Are there any safety issues?

This is uncertain because insufficient research data are available. It is advised that people with asthma be monitored by a healthcare professional. Males with low sperm counts or poor sperm motility should avoid this herb if attempting to father a child.

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Aloe vera

HISTORICAL NOTE *Aloe vera* has been used since ancient times as a medicinal plant. In fact, evidence of use has been found on a Mesopotamian clay tablet dating back to 2100 BC (Atherton 1998). It has been used as a topical treatment for wounds, burns and other skin conditions and internally as a general tonic, anti-inflammatory agent, carminative, laxative, aphrodisiac and anthelmintic by the ancient Romans, Greeks, Arabs, Indians and Spaniards. According to legend, Alexander the Great captured an island in the Indian Ocean in order to access the *Aloe vera* for his wounded army. Today aloe is used to soothe skin complaints and heal burns, and is one of the most common ingredients in many cosmetic products.

OTHER NAMES
Aloes, Barbados aloe, Curacao aloe

BOTANICAL NAME/FAMILY
Aloe vera (L.)/*Aloe barbadensis* (Mill.) (family Aloeaceae)

PLANT PARTS USED
The leaf, from which several different products are made; namely the exudate, gel, extract and juice. The exudate ('aloes' in older pharmacy texts) is a thick residue, yellow in colour and bitter in taste that comes from the latex that oozes out when the leaf is cut. The 'gel' refers to the clear gel or mucilage produced by the inner parenchymal cells in the central part of the leaf. Diluted aloe gel is commonly known as 'aloe vera extract' or 'aloe juice'.

CHEMICAL COMPONENTS
Aloe vera extract, or diluted aloe gel, is made of mostly water (99%) and mono- and polysaccharides, the most important of which are the monosaccharide mannose-6-phosphate and the polysaccharide gluco-mannans, which are long-chain sugars containing glucose and mannose. Gluco-mannan has been named acemannan and is marketed as Carrisyn. A glycoprotein with anti-allergic properties has also been isolated, and has been named alprogen. Recently, C-glucosyl chromone, an anti-inflammatory compound, has also been identified.

Aloe gel also contains lignans, saponins, salicylic acid, sterols and triterpenoids, vitamins A, C, E, B_{12}, thiamine, niacin and folic acid, and the minerals sodium, calcium, potassium, manganese, magnesium, copper, chromium, zinc and iron (Shelton 1991, Yamaguchi et al 1993).

The fresh gel contains glutathione peroxidase, isozymes of superoxide dismutase, and the proteolytic enzyme carboxypeptidase (Klein & Penneys 1988, Sabeh et al 1993). Recent in vitro bioassays identified three malic acid acylated carbohydrates from the gel, veracylglucan A, B and C, and determined that veracylglucan B exhibited potent anti-inflammatory and anti-proliferative effects; veracylglucan C exhibited significant cell proliferative and anti-inflammatory activities; and the third carbohydrate veracylglucan A was highly unstable and provided no biological effects. Of interest is that veracylglucan B and C proved to be highly competitive in their effects on cell proliferation (Esua et al 2006).

Ultimately, the types and levels of components present in aloe gel vary according to geographic origin, variety and processing method.

The exudate (latex layer) contains the pharmacologically active anthraquinone glycosides: aloin, aloe-emodin, barbaloin, emodin and aloectic acid (Choi & Chung 2003, Rodriguez-Fragoso et al 2008).

MAIN ACTIONS
The active ingredients, whether acting alone or in concert, include glycoproteins, anthraquinones, polysaccharides, and low-molecular-weight species such as beta-sitosterol (Choi & Chung 2003).

Assists in wound healing
Wound healing is associated with various mechanisms and constituents. Thromboxane inhibits wound healing and aloe has been shown to inhibit thromboxane in vitro (Zachary et al 1987). Enzymes in aloe have also been shown to break down damaged tissue, which can then be removed by phagocytosis (Bunyapraphatsara et al 1996). A glycoprotein fraction was found to increase proliferation of human keratinocytes and increase the expression of receptors for epidermal growth factor

and fibronectin in vitro (Choi et al 2001). The same research team then demonstrated that this glycoprotein enhanced wound healing by increasing cell proliferation in vivo. Beta-sitosterol appears to improve wound healing by stimulating angiogenesis and neovascularisation in vivo (Moon et al 1999). Aloe polysaccharides have been shown to ameliorate UV-induced immunosuppression (Strickland et al 1994).

Tests in animal models

Several animal studies support the application of aloe gel to skin damaged by frostbite as a means to maintain circulation and reduce the vasoconstrictive effects of thromboxane in the affected dermis (Heggers et al 1987, Klein & Penneys 1988, McCauley et al 1990, Miller & Koltai 1995). In combination with pentoxifylline, it will act synergistically to further increase tissue survival (Miller & Koltai 1995).

A study to test the effectiveness of topical application versus oral administration in rats with full-thickness wounds showed topical use of aloe gel to be slightly more effective than internal use. The collagen content in granulation tissue was measured to be 89% in the topical group compared with 83% in the oral group (Chithra et al 1998). Other studies have found that aloe gel not only increases collagen content, but also changes collagen composition, in addition to increasing collagen cross-linking, which in turn increases the breaking strength of scar tissue, making the seal stronger (Chithra et al 1998, Heggers et al 1996).

Full thickness hot-plate burns (3% total surface area) in test animals healed more quickly with the application of aloe gel compared to silver sulfadiazine (SSD) or salicylic acid cream (aspirin) (Rodriguez-Bigas et al 1988). Guinea pigs treated with aloe recovered in 30 days as compared to 50 days for control animals (dressing only) and wound bacterial counts were effectively decreased. *A. vera* was also found to promote healing and decrease inflammation in second-degree burns in vivo (Somboonwong et al 2000). A significant reduction in vasodilation and post-capillary venular permeability was recorded on day 7 in the aloe group. At day 14 arteriolar diameter had returned to normal and the size of the wound was greatly reduced as compared to controls.

Aloe gel prevented delayed hypersensitivity of UV-irritated skin as well as contact hypersensitivity in animal models with allergic reactions (Strickland et al 1994). Acemannan gel (beta-(1,4)-acetylated mannan) has demonstrably improved radiation burns in mice. Best results were obtained when the gel was applied during the first week after injury (Roberts & Travis 1995).

Use with pharmaceutical agents

Several topical pharmaceutical antimicrobial agents, such as SSD, inhibit wound contraction, thereby slowing the rate of wound healing. An experimental model was used to investigate whether co-administration of aloe could reverse this effect and improve wound-healing rate (Muller et al 2003). Full-thickness excised wounds were treated with placebo (aqueous cream or saline), SSD cream 0.5%, 1% or 1% with *A. vera* three times daily for 14 days, then observed until healed. *A. vera* was found to reverse the delayed wound healing produced by SSD, resulting in the shortest wound half-life and healing time.

A. vera (100 and 300 mg/kg daily for 4 days) blocked the ability of hydrocortisone acetate to suppress wound healing by up to 100% (Davis et al 1994a). Growth factors in *A. vera* were thought to mask sterols and certain amino acids that prevent wound healing. An earlier study identified the sugar mannose-6-phosphate to be one of the chief constituents responsible for wound healing (Davis et al 1994b).

Antioxidant

Studies have found that several compounds present in aloe gel protect tissues against oxidative damage caused by free radicals ('t Hart et al 1990, Singh et al 2000, Wu et al 2006, Yagi et al 2002, Zhang et al 2006). This is achieved by direct antioxidant activity and indirect activity through stimulation of endogenous antioxidant systems. Two aloe dihydroisocoumarins have been identified and have demonstrated free radical scavenging properties (Zhang et al 2006, Zhang et al 2008).

Treatment with aloe gel extract decreased lipid peroxidation and hydroperoxides in diabetic rats to near normal levels (Rajasekaran et al 2005). The extract also significantly increased superoxide dismutase, catalase, glutathione peroxidase and glutathione-S-transferase in the liver and kidney. In another study, data obtained 3, 7 and 10 days after exposure to radiation showed that aloe gel significantly reduced oxidative damage in the liver, lungs, and kidney tissues of irradiated rats (Saada et al 2003).

Three-year-old aloe plants appear to have the highest amounts of flavonoids and polysaccharides and hence the best free radical scavenging capacity, as compared to 2- and 4-year-old plants (Hu et al 2003). Interestingly, the 3-year-old plant demonstrated antioxidant activity of 72.19%, compared to alpha-tocopherol at 65.20%.

Immunostimulant

It has been suggested that aloe may have immune-stimulating capabilities. Much of the available research has been performed on mice or in vitro and aloe shows antiviral, antitumour and non-specific immunostimulant activity. An experiment in 1980 demonstrated that mice given aloe extract 2 days before exposure to pathogens were protected against a variety of fungi and bacteria (Brossat et al 1981). Later, the isolated compound acemannan (beta-(1,4)-acetylated mannan) was shown to increase the response of lymphocytes to antigens in vitro (Womble & Helderman 1988). In mice, acemannan stimulated cytokines, bringing about an immune attack on implanted sarcoma cells, leading to necrosis and regression of cancer cells (Peng et al 1991). A later trial investigated the effects of acemannan on mouse macrophages (Zhang & Tizard 1996). Acemannan stimulated macrophage cytokine production (IL-6 and TNF-alpha), NO release, surface

Clinical note — Wound-healing models
Acute wound healing occurs in four stages that tend to overlap: haemostasis, inflammation, proliferation and remodelling. Underlying metabolic disturbances and/or disease may disrupt the regenerative process, causing delayed healing. Much investigation is conducted with in vitro assays based on cell culture models of the various phases of healing, which provides information about possible mechanisms of action. Experimental models using animals are undertaken to determine the reduction of wound size (usually in terms of area) and hence the rate of healing. Histological examination of granulation and epidermal tissues provides a concurrent analysis at the molecular level. Human models of wound healing provide an opportunity to observe a variety of healing disorders that are less predictable than their cell or animal-based counterparts. *Aloe vera* is the only traditional wound healing herbal medicine that has been subjected to a variety of cell culture-based, animal and human-based studies (Krishnan 2006).

molecule expression, and cellular morphologic changes. Similarly, a polysaccharide fraction isolated from *A. vera* promoted human keratinocytes to secrete TGF-alpha, TGF-beta-1, IL-1-beta, IL-6, IL-8 and TNF, and inhibited the release of NO as compared to control (Chen et al 2005). The immune enhancing effects of acemannan may be due in part to the compound's ability to promote differentiation of immature dendritic cells (Lee et al 2001). These cells are crucial for the initiation of primary immune responses.

Multiple studies have highlighted the diverse immunomodulatory activities of aloe polysaccharides. Recent research has identified that immunomodulatory activity varies with the size of the polysaccharide entity. It appears that aloe polysaccharides that are of smaller molecular weight (specifically between 5 and 400 kDa) have the greatest immunological effects possibly because they are better absorbed than larger MW entities (Im et al 2005).

Three purified polysaccharide fractions (PAC-I, PAC-II and PAC-III) from *A. vera* stimulated peritoneal macrophages, and splenic T and B cells, and increased the ability of these cells to secrete TNF-alpha, IL-1-beta, IFN-gamma, IL-2 and IL-6 (Leung et al 2004). The compound with the highest mannose content, and therefore the highest molecular weight (PAC-I), demonstrated the most potential. This finding was again repeated by Liu et al (2006) whereby PAC-I exhibited potent stimulation of murine macrophages and produced tumouricidal properties of activated macrophages in vitro, thus providing evidence in support of its antitumour properties.

A 99% pure carbohydrate compound (purified acemannan) isolated from aloe demonstrated potent haematopoietic and haematologic activity in myelosuppressed mice (Talmadge et al 2004).

Specific manufacturing methods can be applied to enhance the extracts. For example, 1 g of extract obtained from leaves subjected to cold and dark treatment contained 400 mg of neutral polysaccharide compared with 30 mg in leaves not specially treated (Shida et al 1985).

Anti-inflammatory

A number of in vitro and in vivo studies confirm the anti-inflammatory activity of *A. vera*.

The gel reduces oxidation of arachidonic acid, thereby reducing PG synthesis and inflammation (Davis et al 1987). It inhibits the production of PGE_2 by 30% and IL-8 by 20%, but has no effect on thromboxane B2 production in vitro (Langmead et al 2004). Following burn injury in vivo, *A. vera* was also found to inhibit inflammation by reducing leukocyte adhesion and decreasing the pro-inflammatory cytokines TNF-alpha and IL-6 (Duansak et al 2003).

One study conducted on rats with croton oil-induced oedema reported a 47% reduction in swelling after the application of topical aloe gel (Davis et al 1989). Another study found aloe gel to reduce vascularity and swelling by 50% in the inflamed synovial pouch in rats, along with a 48% reduction in the number of mast cells in the synovial fluid within the pouch. When aloe gel was applied topically there was also an increase in fibroblast cell numbers (Davis et al 1992). C-glucosyl chromone, isolated from aloe gel extracts, is chiefly responsible for the anti-inflammatory effect, with activity comparable to hydrocortisone in experimental models (Hutter et al 1996). A study of streptozotocin-induced diabetic mice further confirmed the anti-inflammatory activity of *A. vera* and identified the isolated constituent gibberellin as also effective (Davis & Maro 1989). Both compounds inhibited inflammation in a dose-dependent manner. A recent in vitro assessment using human immune cells displayed aloe's potential to reduce bacteria-induced pro-inflammatory cytokine production, specifically TNF-alpha and IL-1-beta, by peripheral blood leukocytes stimulated with *Shigella flexneri* or lipopolysaccharide (LPS) (Habeeb et al 2007a).

Laxative

The aloe latex contains anthraquinones, which have a stimulant laxative activity. Studies in rats have shown that aloe latex increases intestinal water content, stimulates mucus secretion, and induces intestinal peristalsis (Ishii et al 1994). However, aloe as a laxative is more irritating than other herbs (Reynolds & Dweck 1999) and long-term use can cause an electrolyte imbalance through depletion of potassium salts. Alternatives are recommended if long-term treatment is required.

Anti-ulcer

The anti-ulcer activity of *A. vera* has been proposed to be due to anti-inflammatory, cytoprotective, healing and mucus stimulatory effects. According to an in vivo study, *A. vera* promotes gastric ulcer healing (Eamlamnam et al 2006). In contrast to these results, in another study a stabilised fresh aloe gel preparation

prolonged the effect of histamine-stimulated acid secretion but inhibited pepsin (Suvitayavat et al 2004).

Hypoglycaemic

Glucomannan slows carbohydrate absorption and slows the postprandial insulin response by up to 50% (McCarty 2002).

A. vera leaf gel has been investigated as a possible hepatoprotective and kidney protective agent in diabetes type 2 using animal models. In one study, the leaf gel and glibenclamide both decreased degenerative kidney changes, serum urea levels and creatinine levels, but only aloe further reduced kidney lipid peroxidation (Bolkent et al 2004). Can et al (2004) tested aloe pulp, aloe gel extract and glibenclamide, finding that all treatments decreased liver tissue damage compared to control animals. Aloe gel extract also increased glutathione levels and decreased non-enzymatic glycosylation, lipid peroxidation, serum alkaline phosphatase and alanine transaminase.

Antimicrobial

A. vera is active against a wide variety of bacteria in vitro, such as *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Streptococcus pyogenes*, *Staphylococcus aureus* and *Escherichia coli* (Heck et al 1981, Shelton 1991). More recent research indicates antimicrobial activity against *Shigella flexneri*, methicillin-resistant *Staphylococcus aureus* (MRSA), *Enterobacter cloacae* and *Enterococcus bovis* (Habeeb et al 2007a).

Antiviral

In vitro studies suggest that *Aloe vera* has antiviral activity due to its interference with DNA synthesis (Saoo et al 1996). The polysaccharide fractions of aloe gel inhibit the binding of benzopyrene to primary rat hepatocytes and thus prevent the formation of potentially cancer-initiating benzopyrene-DNA adducts in vitro. This was later confirmed by in vivo studies (Kim & Lee 1997). Moreover, in vitro experiments have shown the anthraquinones in aloe to be virucidal against HSV 1 and 2, vaccinia virus, parainfluenza virus and vesicular stomatitis virus (Anderson 2003).

Investigation with the acemannan component has identified antiviral activity, particularly against feline AIDS, HIV type 1, influenza virus, measles virus and herpes simplex (Kahlon et al 1991a & b, Sydiskis et al 1991).

CLINICAL USE

Although *A. vera* products are used for many indications, the chief use is treating skin conditions.

Skin conditions

Aloe is used in the treatment of wounds, burns, radiation burns, ulcers, frostbite, psoriasis and genital herpes, and is the only traditional wound-healing herbal medicine which has been subjected to a variety of cell culture-based, animal and human-based studies (Krishnan 2006). The healing properties may be attributed to antimicrobial, immune-stimulating, anti-inflammatory and antithromboxane activities. Allantoin has also been shown to stimulate epithelialisation, and acemannan has been shown to stimulate macrophage production of IL-1 and TNF, which are associated with wound healing (Liptak 1997).

Most human studies have found that topical application of aloe vera gel increases wound healing rate and effectively reduces microbial counts; however, there are some negative studies, most likely related to the fact that the composition of aloe vera gel varies, even within the same species. Chemical composition depends on source, climate, region, and the processing method used (Choi & Chung 2003).

Dry-coated aloe vera gloves were tested by 30 women suffering from dry, cracked hands, with or without contact dermatitis due to occupational exposure, in an open contralateral comparison study (West & Zhu 2003). Women wore a glove on one hand for 8 hours daily for 30 days followed by a rest period for 30 days and then 10 more days of treatment. Results indicated that the aloe vera glove significantly reduced dry skin, irritation, wrinkling, dermatitis, redness and improved skin integrity. It would be interesting to see this study repeated using a standard non-aloe fortified glove on the opposing hand.

The effects of aloe gel applied to skin following dermabrasion in humans are more controversial, with some patients responding well (Fulton 1990), while others have had severe adverse reactions, including burning sensations and dermatitis (Hunter & Frumkin 1991). A standard polyethylene oxide gel dressing saturated with stabilised aloe vera gel was compared to the standard oxide dressing alone in the study by Fulton and appears to exhibit the strongest evidence overall to support the beneficial effects of *A. vera*. The addition of *A. vera* produced a significant vasoconstriction and anti-inflammatory effect 24 and 48 hours after application. By the 4th day it produced less crusting and exudate and by the 5th and 6th day re-epithelialisation was almost complete (90% for aloe compared with 50% for the standard treatment). Overall, wound healing was quicker with *A. vera* and completed by an average of 72 hours before the oxide gel-treatment. In contrast, one study found that topical aloe vera gel actually slowed healing after caesarean delivery (Schmidt & Greenspoon 1991).

Burns

A recent systematic review of the efficacy of *A. vera* for healing of burns considered four controlled clinical trials involving 371 patients. Meta-analysis concluded that topical treatment with *A. vera* decreased healing time and was specifically more effective for first- and second-degree burns rather than third-degree. It was noted that due to variations in the aloe preparations and outcome measures used in the studies, more specific conclusions cannot be drawn (Maenthalsong et al 2007).

One study involving 27 patients with a partial-thickness burn injury found that topical aloe gel significantly increased the healing rate compared with controls who used a vaseline gauze. The mean healing time for the aloe gel group was 11.89 days compared with the control group, which was 18.18

days. Additionally, the aloe treatment brought about full epithelialisation after 14 days (Visuthikosol et al 1995).

Another study involving 18 outpatients with moderate to deep second-degree burns ranging from 2 to 12% of total body surface area showed that a commercial aloe vera ointment was as effective as SSD in regard to protection against bacterial colonisation and healing time. More specifically, the mean healing time with aloe vera treatment was 13 days compared with 16.15 days for SSD (Heck et al 1981).

Results are less encouraging for sunburn protection and healing. A randomised double-blind trial in 20 healthy volunteers evaluated the effect of aloe vera cream for both prevention and treatment of sunburn (Puvabanditsin & Vongtongsri 2005). The cream (70% aloe) was applied 30 minutes before, immediately after, or both before and after UV irradiation. The cream was then continually applied daily for 3 weeks. The results showed that the aloe vera cream did not protect against sunburn and was not an effective treatment.

Frostbite

In combination with other treatments, topical *A. vera* significantly enhances healing and has a beneficial effect in frostbite. One clinical study compared the effects of topical aloe vera cream in combination with standard treatment, such as rapidly rewarming the affected areas, analgesics, antibiotics and debridement ($n = 56$) with another group of 98 patients who did not receive *A. vera* treatment. Of those receiving *A. vera* in addition to usual treatment, 67% healed without tissue loss compared with 32.7% in the control group. Additionally, 7.1% of the total group of 56 required amputation compared with 32.7% in the control group. Although encouraging, this study is difficult to interpret because the groups were not well matched and combination therapies differed (Heggers et al 1987).

Radiation-induced dermatitis

A recent review concluded that aloe gel was as effective as mild steroid creams, such as 1% hydrocortisone, in reducing the severity of radiation burn, without the side-effects associated with steroid creams (Maddocks-Jennings et al 2005). In contrast, another review concluded that aloe was ineffective for the prevention or reduction of side-effects to radiation therapy in cancer patients (Richardson et al 2005). That review analysed 1 past review, 5 published RCTs and 2 unpublished RCTs. It is important to note that various preparations such as creams, juices, gels and fresh aloe had been tested, which makes it difficult to assess the evidence.

Ulcers

A number of case reports tell of a positive effect on leg ulcers with topical use of aloe gel, including cases that did not respond to standard medical interventions (Zawahry et al 1973). Application of water-based aloe-gel saline soaks, broad-spectrum antibiotics and antifungals allowed a wound, caused by necrotising fasciitis, to heal in 45 days in a 72-year-old woman. Aloe gel and saline-soaked sponges were also used to treat two large seroma cavities caused by deep vein thrombosis in a 48-year-old man (Ardire 1997).

Although aloe gel is commonly used as a topical agent for wound healing it is also used internally. A small study of six patients with chronic leg ulcers found that ingesting 60 mL aloe juice daily and applying aloe gel directly to the ulcer and surrounding area resulted in less exudate, odour and seepage through the bandaging (Atherton 1998).

Psoriasis

A double-blind placebo-controlled study found topical aloe vera extract 0.5% in a hydrophilic cream to be beneficial in the treatment of psoriasis. Sixty patients aged 18–50 years with slight to moderate chronic psoriasis and PASI (psoriasis area and severity index) scores between 4.8 and 16.7 (mean 9.3) participated in the study, which was scheduled for 16 weeks with 12 months of follow-up. Patients were examined weekly and those showing a progressive reduction of lesions, desquamation followed by decreased erythema, infiltration and lowered PASI score were considered healed. By the end of the study, the *A. vera* extract cream had cured 83.3% of patients compared with the placebo cure rate of 6.6% ($P < 0.001$). Psoriatic plaques decreased in 82.8% of patients versus only 7.7% in the placebo group ($P < 0.001$). PASI scores decreased to a mean of 2.2 (Syed et al 1996a). In contrast, a randomised, double-blind, placebo-controlled trial found no significant benefits with a commercial aloe vera gel in 41 patients with stable plaque psoriasis (Paulsen et al 2005). Following a 2-week washout period patients applied either the aloe gel or placebo twice daily for 1 month. Redness and desquamation decreased by 72.5% in the active treatment group as compared to 82.5% in the placebo group. It should be pointed out that 82.5% is an extremely high placebo responder rate. Fifty-five per cent of patients reported local side-effects, mainly drying of the skin on test areas.

Genital herpes

Two clinical studies have investigated the effects of *Aloe vera* 0.5% topical preparations in genital herpes, producing good results.

A double-blind, placebo-controlled study has demonstrated that *A. vera* extract 0.5% in a hydrophilic cream is more efficacious than placebo in the treatment of initial episodes of genital herpes in men ($n = 60$, aged 18–40 years). Each patient was provided with a 40 g tube, containing placebo or active preparation with instructions on self-application of the trial medication to their lesions three times daily for 5 consecutive days (maximum 15 topical applications per week). The treatment was well tolerated by all patients (Syed et al 1997).

The other study involving 120 subjects used a preparation containing 0.5% of whole aloe leaf extract in a hydrophilic castor and mineral oil cream base, which was applied three times daily for 5 days per week for 2 weeks. Treatment resulted in a shorter mean duration of healing compared with

placebo. Aloe cream also increased the overall percentage of healed patients and there were no significant adverse reactions reported (Syed et al 1996b).

HIV

The acemannan component of *Aloe vera* has been used as adjunctive therapy to antiretroviral therapy in HIV infection. A preliminary clinical trial found that acemannan may enhance the activity of the anti-HIV drug AZT. A dose of 800 mg acemannan daily significantly increased circulating monocytes (macrophages) in 14 HIV patients. Aloe increased the number and activity of the monocytes (McDaniel et al 1990). Subsequently, a randomised, double-blind placebo-controlled study of 63 male subjects with advanced HIV, taking zidovudine and didanosine, investigated the effects of 400 mg of acemannan taken four times daily for 48 weeks. Results showed a decrease in CD4 cell numbers in the acemannan group compared with placebo (Montaner et al 1996).

Gastrointestinal conditions

Oral *A. vera* is a popular treatment for a variety of gastrointestinal disorders. It has been shown to improve different parameters of gastrointestinal function in normal subjects, such as colonic bacterial activity, gastrointestinal pH, stool specific gravity and gastrointestinal motility (Bland 1986). Due to its anthraquinone content, the latex is used as a stimulant laxative.

Besides this indication, there is still a need for scientific validation to establish which gastrointestinal conditions are most receptive to treatment with aloe.

Irritable bowel syndrome

A. vera may be effective for patients with diarrhoea-predominant IBS, according to a randomised, placebo-controlled study ($n = 58$) (Davis et al 2006). Both treatments were administered for 1 month with a follow-up period of 3 months. Within the first month, 35% of the patients receiving *A. vera* responded compared to 22% receiving placebo. Overall, diarrhoea-predominant IBS patients had a more statistically significant responder rate than placebo (43% vs 22%).

Ulcerative colitis

A double-blind, randomised, placebo-controlled trial evaluated the efficacy and safety of *A. vera* gel (100 mL twice daily for 4 weeks) in ulcerative colitis (Davis et al 2006). Aloe induced clinical remission in 30% of subjects compared to 7% for placebo and symptom improvement in 37% compared to 7% for placebo. The Simple Clinical Colitis Activity Index and histological scores also decreased significantly for patients on the aloe treatment, but not for those receiving placebo.

OTHER USES

Asthma

According to a small open study ($n = 33$), long-term oral administration of aloe may have benefits for some people with chronic asthma, as one-third of subjects reported improvement (Afzal et al 1991, Shida et al 1985).

Diabetes

Glycaemic control

Three systemic reviews of herbal medicines for glycaemic control in diabetes found that *A. vera* can lower blood glucose levels in diabetic patients (Grover et al 2002, Vogler & Ernst 1999, Yeh et al 2003). In one trial aloe juice consisting of 80% gel or placebo was given in a trial of 40 patients who were recently diagnosed with type 1 diabetes at the dose of 1 tablespoon twice daily. From day 14 the blood sugar levels in the aloe group began to fall significantly compared with the control group and continued to steadily drop during the study period ($P < 0.01$). Blood triglyceride levels were also substantially reduced but cholesterol levels remained the same (Yongchaiyudha et al 1996). A single-blind, placebo-controlled trial found that glibenclamide when combined with oral aloe gel was more effective in reducing blood sugar levels than glibenclamide alone in 72 patients with type 2 diabetes. Patients took 5 mg of glibenclamide twice daily and 1 tablespoon aloe gel. Fasting blood glucose levels dropped appreciably after just 2 weeks of treatment, and were still falling after 42 days (Bunyapraphatsara et al 1996).

Cancer

There are some epidemiological studies suggesting that aloe may reduce the risk of certain cancers; however, further research is required to clarify its place in practice (Sakai et al 1989, Siegers et al 1993).

Recent pre-clinical research has identified that aloe-emodin (an anthraquinone compound) present in the leaves of *A. vera* shows promising anticancer effects in human gastric carcinoma cell lines AGS and NCI-N87. A.-emodin induced cell death in a dose-dependent and time-dependent manner and caused the release of apoptosis-inducing factor and cytochrome c from mitochondria followed by the activation of caspase-3 leading to nuclear shrinkage and apoptosis (AGS was more sensitive that NCI-N87 cells). In addition, casein kinase II activity was suppressed (time-dependent) and was accompanied by a reduced phosphorylation of Bid, a downstream substrate of casein kinase II and a pro-apoptotic molecule (Chen et al 2007).

Another study investigated the anticancer effect of aloe-emodin in T24 human bladder cancer cells and found that it induced apoptosis in T24 cells mediated through the activation of p53, p21, Fas/APO-1, Bax and caspase-3 (Lin et al 2006).

Chemotherapy-induced oral and gastrointestinal mucositis

Aloe gel may ameliorate chemotherapy-induced oral and gastrointestinal mucositis (Stargrove et al 2008), however, the evidence base is conflicting and further research is required.

DOSAGE RANGE

- Aloe vera gel: fresh from a living plant or as stabilised juice 25 mL (4.5:1) up to four times daily.
- Extracts standardised to acemannan: preparation containing up to 800 mg/day.
- Topical application: gel, cream or ointment as needed.
- 1.5–4.5 mL daily of 1:10 tincture of resin (latex).

ADVERSE REACTIONS

Although adverse reactions are rare, hypersensitivities and contact dermatitis to aloe have been reported (Morrow et al 1980, Nakamura & Kotajima 1984). Hypersensitivity manifested by generalised nummular eczematous and papular dermatitis, and presumably by contact urticaria, developed in a 47-year-old man after 4 years of using oral and topical aloe. Patch tests for aloe were positive in this patient (Morrow et al 1980).

SIGNIFICANT INTERACTIONS

Hypoglycaemic agents

Oral *A. vera* may have hypoglycaemic activity, therefore additive effects are theoretically possible—observe patients taking this combination.

Laxatives

Additive effects are theoretically possible with oral aloe latex inducing griping pains. Use with caution.

Topical cortisone preparations

In addition to its own anti-inflammatory effects, animal studies have shown that *A. vera* increases the absorption of hydrocortisone by hydrating the stratum corneum, inhibits hydrocortisone's suppressive effects on wound healing and increases wound tensile strength — possible beneficial interaction.

Vitamins C and E

Concurrent prescription of oral *A. vera* (both gel and latex) with vitamins C and E shows improved absorption and increased plasma life of vitamin concentration for both vitamins when taken together (Vinson et al 2005).

CONTRAINDICATIONS AND PRECAUTIONS

Strong laxatives such as aloe latex are contraindicated in children. Avoid in patients with known hypersensitivity to aloe or with nausea, vomiting or signs and symptoms of gastrointestinal obstruction. Avoid excessive use and long-term use (more than 2 weeks), as potassium losses may occur, which may alter cardiac electrophysiology.

Use with caution in people with thyrotoxicosis.

A case study of depression of thyroid hormones in a woman taking *A. vera* juice has been reported (Pigatto & Guzzi 2005). The patient consumed 10 mL daily for 11 months and laboratory testing showed reduced levels of thyroxine and triiodothyronine. Levels returned to normal progressively after discontinuing the aloe juice and the patient achieved full clinical remission after 16 months. Reduced serum levels of the thyroid hormones T_3 and T_4 have been reported for *A. vera* in vivo (Kar et al 2002).

PRACTICE POINTS/PATIENT COUNSELLING

- Different parts of the *Aloe vera* plant are used therapeutically. The gel is used topically and the latex is used internally.
- The gel may be beneficial in the treatment of skin conditions (wounds, burns, radiation burns, ulcers, frostbite, psoriasis and genital herpes). There is good scientific evidence for these indications.
- Traditionally, aloe latex is also used internally for gastrointestinal ulcers, dyspepsia and what is known today as IBS. Aloe is also used in conditions such as food allergies and disturbed bowel flora.
- Aloe may be a useful adjunct in the treatment of chronic poor immunity, HIV, cancer and chronic fatigue. There is preliminary scientific support for these indications.

Caution is suggested with topical applications that contain *A. vera* as they may enhance sensitivity to ultraviolet light (Xia et al 2007).

PREGNANCY USE

Strong laxatives such as aloe latex are traditionally contraindicated in pregnancy. Scientific evidence is unavailable to conclusively support the safe use of orally administered aloe.

PATIENTS' FAQs

What will this herb do for me?

Aloe gel is traditionally used for burns, wounds and inflammatory skin disorders. There is good scientific evidence that aloe may be of benefit in these conditions; however, the chemical composition of *A. vera* products will vary depending on geographical and processing factors. Traditionally, aloe is also used internally for dyspepsia, gastrointestinal ulcers and IBS.

When will it start to work?

Aloe has an immediate effect on burns and inflammatory skin diseases. Improvement occurs within several weeks with the condition continuing to improve with use. Chronic conditions may require long-term use. Internal use of *A. vera* as a laxative can produce results within 12–24 hours.

Are there any safety issues?

Aloe gel is safe and non-toxic when used topically. Avoid chronic use of laxative preparations that contain highly irritant compounds, known as anthraquinone glycosides, in the latex.

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Andrographis

HISTORICAL NOTE Andrographis has long been used in traditional medicine systems in numerous countries. It has been included in the pharmacopoeias of India, Korea and China, possibly because it grows abundantly in India, Pakistan and various parts of Southeast Asia. In TCM, andrographis is considered a 'cold' herb and is used to rid the body of heat, as in fevers and acute infections, and to dispel toxins from the body. In Ayurvedic medicine it is used as a bitter tonic, to stimulate digestion and as a treatment for a wide range of conditions such as diabetes and hepatitis. It is still a common household remedy and found in more than half the combination tonics used to treat liver conditions in India. Also used to treat the common cold, it is sometimes called Indian echinacea.

COMMON NAMES
Andrographis, chirayata, chiretta, green chiretta, Indian echinacea, kalmegh, king of bitters. *Andrographis paniculata* is often studied as the herbal combination known as Kan Jang.

BOTANICAL NAME/FAMILY
Andrographis paniculata (family Acanthaceae)

PLANT PARTS USED
Leaves, aerial parts

CHEMICAL COMPONENTS
The main active constituent group is considered to be the bitter diterpenoid lactones known as andrographolides. This group consists of andrographolide (AP1), 14-deoxy-11,12-didehydroandrographolide (AP3) and neoandrographolide (AP4). Other constituents include diterpenoid glucosides, diterpene dimers, flavonoids (Koteswara et al 2004, Rao et al 2003) and xanthones (Dua et al 2004).

Clinical studies show that andrographis is well absorbed, with peak plasma concentrations reached after 1.5–2 hours and a half-life of 6.6 hours (Panossian et al 2000).

MAIN ACTIONS
The mechanism of action of andrographis has not been significantly investigated in clinical studies, so results from in vitro and animal tests provide most of the evidence for this herbal medicine.

Immunomodulating
According to in vivo research, andrographis stimulates both antigen-specific and non-specific immune responses (Puri et al 1993). One of the main constituents responsible for the immunostimulant activity is andrographolide, which has an effect on the stimulation and proliferation of immunocompetent cells and the production of key cytokines and immune markers in vitro (Panossian et al 2002). Although important, other pharmacologically active constituents are also present, as demonstrated by a study that found that the immunostimulant activity of the whole extract is greater than that of the isolated andrographolide constituent alone. Investigation with a combination of the whole extract and *Eleutherococcus senticosus* in the formula Kan Jang demonstrated a more profound effect.

Andrographolide was found to decrease IFN-gamma and IL-2 production and was therefore shown to have an immunosuppressive effect. Burgos et al (2005) concluded that andrographis may be useful for autoimmune disease, especially where high levels of IFN-gamma are present, for example in multiple sclerosis and RA. In vitro and in vivo data has recently shown that andrographolide has the ability to interfere with T-cell proliferation, cytokine release and maturation of dendritic cells, as well as to drastically decrease the antibody response in delayed-type hypersensitivity (Iruretagoyena et al 2005). Additionally, andrographolide demonstrated a capacity to inhibit T-cell and antibody responses in experimental autoimmune encephalomyelitis in mice, and to protect against myelin sheath damage.

Anticancer
In vitro experiments have demonstrated the possible benefits of andrographolide on various cancer cells. The compound has been shown to increase apoptosis of prostate cancer cells and human leukaemic cells and to increase cell-cycle arrest (Cheung et al 2005, Geethangili et al 2008, Kim et al 2005, Zhao et al 2008, Zhou et al 2006). It also inhibits the proliferation of human cancer cells and increases IL-2 induction in human peripheral blood lymphocytes in vitro (Kumar et al 2004, Rajagopal et al 2003). In vivo results show that andrographolide increases IL-2, interferon-gamma and T-cell activity (Sheeja et al 2007). In certain circumstances, andrographolide has been found to decrease IFN-gamma and IL-2 and may have an immunosuppressive effect (*see Immunomodulating* above).

Andrographis and andrographolide may also inhibit angiogenesis and cancer cell adhesion (Sheeja et al 2007, Jiang et al 2007).

Antimicrobial
Aqueous extract of *A. paniculata* has demonstrated significant antibacterial and antifungal activity in vitro when compared with standard antibiotics (Singha et al 2003). The andrographolides from andrographis have displayed antiviral activity against herpes simplex virus type 1 in vitro (Wiart et al 2005).

Antimalarial
In vitro and in vivo studies have identified considerable antimalarial effects (Najib et al 1999, Siti Najila et al 2002). Administration of andrographis immediately after infection and for an additional 4 days extended the life span of mice infected with *Plasmodium berghei* strain ANKA (Rahman et al 1999). Four xanthones recently isolated from *A. paniculata* have demonstrated antimalarial activity against *Plasmodium berghei* in vivo (Dua et al 2004). Treatment with 30 mg/kg for 4 days produced a 62% decrease in parasites in infected mice.

Cardiovascular effects
Several in vivo studies have suggested a potential role for andrographis in cardiovascular disease.

- **Prevention of atherosclerotic arterial stenosis and restenosis after angioplasty.** According to two animal studies, andrographis significantly improved atherosclerotic iliac artery stenosis induced by both de-endothelialisation and a high-cholesterol diet, and reduced the re-stenosis rate after experimental angioplasty (Wang & Zhao 1993, 1994).
- **Prevention of myocardial reperfusion injury and postoperative malignant arrhythmias.** Using an animal model, pretreatment with intravenous andrographis significantly protected the myocardium from ischaemic reperfusion injury and eliminated malignant arrhythmia development after reperfusion, compared with controls (Guo et al 1996). As a result of treatment, infarct size was also smaller and myocardial damage was lessened.
- **Hypertension.** Andrographis produced significant dose-dependent falls in mean arterial blood

pressure and heart rate when administered as an intraperitoneal infusion in one animal study (Zhang et al 1998). This study suggests a mechanism of action involving adrenoceptors, autonomic ganglia receptors and a reduction in circulating ACE. One constituent that appears to be primarily responsible for the herb's hypotensive effects is 14-deoxy-11,12-didehydroandrographolide (AP3) which induces relaxation of vascular smooth muscle and decreases heart rate (Yoopan et al 2007).

Hypoglycaemic

Andrographis has a strong dose-dependent action on insulin production in vitro (Wibudi et al 2008). Another in vitro study indicates that inhibition of alpha-glucosidase may contribute to the hypoglycaemic effects (Subramanian et al 2008). A recent in vivo study in alloxan-induced diabetic rats demonstrated significantly reduced blood glucose levels as compared to placebo (Reyes et al 2006). The authors commented that andrographis may restore impaired oestrous cycle in this model. A previous animal trial concluded that andrographolide (1.5 mg/kg) lowers plasma glucose by enhancing glucose utilisation in diabetic rats (Yu et al 2003). Andrographis may also alter glucose absorption from the gut (Borhanuddin et al 1994). Other in vitro data suggest that andrographolide may also lower plasma glucose by increasing glucose uptake in cultured myoblast cells via the phospholipase C/protein kinase C pathway (Hsu et al 2004).

Hepatoprotective

The hepatoprotective activity of andrographis has been investigated using several different experimental rat models, in which galactosamine, paracetamol and carbon tetrachloride were given to rats to test toxicity (Handa & Sharma 1990a & b, Rana & Avadhoot 1991). In all models, treatment led to complete normalisation of toxin-induced increases in the levels of key biochemical parameters, and significantly reduced toxin-induced histopathological changes to the liver. Andrographolide is one of the key active constituents responsible for this activity (Handa & Sharma 1990b, Rana & Avadhoot 1991). Results from animal studies suggest that the hepatoprotective effect of andrographolide is at least comparable and possibly more potent than that of silymarin, from the herb St Mary's thistle (Rana & Avadhoot 1991, Singha et al 2007, Visen et al 1993).

Analogous to silymarin, the activity is a result of several similar mechanisms working together. Andrographis increases liver superoxide dismutase, glutathione peroxidase, glutathione reductase and catalase concentrations, thereby increasing endogenous antioxidant production by the liver (Trivedi & Rawal 2001, Trivedi et al 2007, Tripathi & Kamat 2007). A hepatocyte cell-membrane-stabilising activity has also been observed (Puri et al 1993, Upadhyay et al 2001).

Digestive stimulant/choleretic

Andrographolide produces a significant dose-dependent increase in bile flow and in bile salt and acid production (Shukla et al 1992).

Antipyretic and anti-inflammatory

Testing in different animal models has identified antipyretic activity (Mandal et al 2001). Clinical testing in randomised double-blind trials involving volunteers with the common cold suggests that this activity is clinically relevant. The mechanism of action is unlike that of NSAIDs, as andrographis does not influence the biosynthesis of any lipoxygenase pathways, but may involve promoting ACTH production and enhancing adrenocortical function (Amroyan et al 1999).

A. paniculata extract completely inhibited inflammation in a carageenan model in vivo (Sheeja et al 2006). In vitro data from the same study showed that andrographis inhibited superoxide (32%), hydroxyl radicals (80%), lipid peroxidation (80%) and nitric oxide (42.8%). These antioxidant mechanisms are likely to contribute to the herb's anti-inflammatory effect.

Antiplatelet and antithrombotic activity

Several compounds found in andrographis inhibit platelet-activating-factor-(PAF)-induced human blood platelet aggregation. These have been identified as andrographolide and AP3; more recently four flavonoids have been isolated that inhibit thrombin and PAF-induced platelet aggregation (Amroyan et al 1999, Wu et al 2008, Thisoda et al 2006). Andrographolide and AP3 inhibit the extracellular signal-regulated kinase 1/2 pathway in vitro. Results from in vivo studies suggest that andrographis prevents the formation of thrombi and reduces the size of myocardial ischaemia by promoting synthesis of prostaglandin I_2, inhibiting production of thromboxane A2, stimulating synthesis of cyclic AMP in platelets, and inhibiting platelet aggregation (Zhao & Fang 1990, 1991). Clinical research in humans has confirmed the observed antiplatelet effect (Zhang et al 1994).

CLINICAL USE

Upper respiratory tract infections (URTI) and the common cold

Although sometimes investigated as a sole treatment, andrographis is also tested as part of a herbal combination known as Kan Jang. This is a standardised formula of *A. paniculata* extract 85 mg, containing 5.25 mg andrographolide and deoxyandrographolide per tablet, and *Eleutherococcus senticosus* extract 9.7 mg, containing total eleutheroside B and eleutheroside E 2% (Melchior et al 2000). Although more representative of real-life practice, results obtained with Kan Jang make it difficult to assess the individual role of andrographis.

Common cold — symptom relief and reduced incidence

In 2004, two different systematic reviews that investigated whether andrographis is a suitable treatment in acute respiratory infections were published (Coon & Ernst 2004, Poolsup et al 2004). The one conducted by Coon and Ernst from the Peninsula Medical School, Universities of Exeter and Plymouth, Exeter, UK, was a review of seven double-blind,

controlled trials (n = 896), from which the authors concluded that *A. paniculata* is more effective than placebo in treating uncomplicated URTI and is associated with relatively few adverse events. They also concluded that preliminary data suggested a protective effect. In five of the seven trials, the daily dose was equivalent to 60 mg of andrographolide, which was administered for 3–8 days.

The second systematic review conducted by Poolsup et al from the Department of Pharmacy, Faculty of Pharmacy, Silpakorn University, Nakhon-Pathom, Thailand, was a review of four randomised controlled trials (n = 433); they came to a similar conclusion, finding that *A. paniculata*, either by itself or in combination with *Eleutherococcus senticosus* (Kan Jang), is effective for uncomplicated acute URTI.

In 2006 another systematic review was released by the Natural Standard Research collaboration (Kligler et al 2006). This review evaluated seven clinical trials (n = 879) that were deemed to be of acceptable quality. Once again, clinical trial evidence was found to be positive but researchers commented that most of the studies have been done in conjunction with a major manufacturer of the product and further independent testing was required.

Symptoms responding

Double-blind studies show that numerous symptoms respond to treatment with andrographis. According to two trials that used a dose of 340 mg andrographis taken three times daily, total symptom scores improved, with throat signs and symptoms responding most strongly (Melchior et al 2000). A third study observed a decrease in rhinitis, sinus pain and headache compared with a placebo (Hancke et al 1995). A fourth study using a treatment dose of 1200 mg andrographis daily found a significant reduction in tiredness and sleepiness, as well as in sore throat and nasal secretions, by day 4 (Caceres et al 1999).

A double-blind placebo-controlled study (n = 185) that tested Kan Jang in the treatment of acute URTI and sinusitis showed it effectively reduced headache, nasal and throat symptoms and general malaise, but had no significant effects on cough and ocular symptoms. Additionally, fever was moderately reduced with active treatment (Gabrielian et al 2002).

Comparisons with echinacea

Although no direct head-to-head study could be located, one study was found that compared the effects of Kan Jang to a product known as Immunal (containing *Echinacea purpurea* [L.] extract) when both were used as adjuncts to standard treatment in children with the common cold. One hundred and thirty children were divided into three groups and received either of the combination treatments or solely standard treatment over a 10-day period (Spasov et al 2004). The addition of Kan Jang was shown to be significantly more effective than Immunal when started at an early stage and produced better symptomatic relief. The amounts of nasal secretion and congestion were particularly improved. With regard to altering recovery time, Kan Jang was also superior to Immunal, and children who received Kan Jang required less standard medication than in the other two groups. Additionally, Kan Jang treatment was well tolerated and no side effects or adverse reactions were reported.

Mediterranean fever

A combination of andrographolide and *Eleutherococcus senticosus*, *Schisandra chinensis* and *Glycyrriza glabra* inhibited neutrophil adhesion and transmigration (Shen et al 2002) and stabilised NO and IL-6 in functional Mediterranean fever according to a randomised, double-blind trial (Panossian et al 2003). The study involved 14 people (aged 3–15 years) with the fever and found that the herbal combination significantly reduced the frequency, severity and duration of attacks (Amaryan et al 2003). The daily dose of andrographolide was 48 mg, divided into 3 doses for 1 month.

Cancer (in combination)

Twenty patients with various end-stage cancers were given 500 mg twice daily for 6 months. After 6 months, 16 patients were still alive with a statistically significant increase in both NK function and TNF-alpha levels. Haemoglobin, haematocrit and glutathione levels were all greatly increased (See et al 2002). Although these results are interesting, it is difficult to examine the direct effect of *A. paniculata*, as many other nutritional supplements were given concurrently.

Pharyngotonsillitis

One randomised double-blind study involving 152 volunteers compared the effects of paracetamol with two different doses of andrographis (3 g and 6 g) taken daily for 7 days (Thamlikitkul et al 1991). By day 3 the symptom-relieving effects of both paracetamol treatment and high-dose *A. paniculata* were significant, and by day 7 andrographis was as effective as paracetamol.

Spermatogenesis

A phase 1 clinical study investigated the effects of Kan Jang (combination of andrographis and *Eleutherococcus senticosus*) on spermatogenesis and fertility in 14 healthy men aged between 18 and 35 years to ensure there were no ill effects (Mkrtchyan et al 2005). The men were randomised into one of five groups to receive either Kan Jang equivalent to 60 mg andrographolide, Kan Jang equivalent to 120 mg andrographolide, Kan Jang equivalent to 180 mg andrographolide, ginseng mixture or valerian extract. They found that Kan Jang was safe if taken at the highest dose, which was three times the therapeutic dose. The researchers discovered that the mixture in fact improved semen quality by increasing the number of healthy, active sperm in the ejaculate.

OTHER USES

Traditional uses

The herb is traditionally given as a restorative and tonic in convalescence and used as a choleretic to stimulate bile production and flow, which improves appetite and digestion. It is often used in combination with aromatic herbs, such as peppermint, for

stronger digestive effects and to prevent gastrointestinal discomfort at higher doses.

Snake bite
Prolonged survival has been reported with intraperitoneal administration of andrographis before administration of cobra venom (Martz 1992).

HIV infection
A phase 1 clinical trial involving non-medicated HIV-positive patients and healthy controls found that oral andrographolides taken for 6 weeks at increasing doses produced no significant benefits and a high incidence of adverse effects, causing the trial to be stopped prematurely (Calabrese et al 2000).

DOSAGE RANGE

URTI
Prevention dose
1200–3000 mg andrographis (standardised to contain no less than 11.2 mg andrographolides) or 4–6 mL of 1:2 liquid extract, daily in divided doses, taken for at least 3 months for preventive effects to become established.

Treatment dose for infection
1200–6000 mg/day or fluid extract (1:2): up to 12 mL/day or equivalent in solid dose form.

Dyspepsia
Andrographis can be taken as a tea before meals: 5 g of herb in 1 cup of hot water, which should be allowed to stand for 10 minutes before drinking.

Toxicity
Animal tests suggest low toxicity (Mills & Bone 2000).

ADVERSE REACTIONS
Generally well tolerated, but high doses may cause vomiting, anorexia and gastrointestinal discomfort. One source states that urticaria is also possible (Ernst 2001).

SIGNIFICANT INTERACTIONS
Controlled studies are not available; therefore, interactions are theoretical and based on evidence of pharmacological activity with uncertain clinical significance.

Anticoagulants
Increased risk of bruising and bleeding is theoretically possible, because andrographolide and other constituents in andrographis inhibit PAF-induced platelet aggregation. However andrographis used together with warfarin did not produce any significant effects on the pharmacokinetics of warfarin, and had even less effect on its pharmacodynamics in vivo (Hovhannisyan et al 2006). Caution should still be exercised until further research is available.

Antiplatelet drugs
Additive effects are possible, because the herb exhibits antiplatelet activity — observe the patient.

Barbiturates
Additive effects are possible, according to an animal study (Mandal et al 2001) — observe the patient. Beneficial interaction is theoretically possible under professional supervision.

Hepatotoxic drugs (paracetamol, tricyclic antidepressants)
Hepatoprotection is possible, according to studies in various experimental models — interaction is beneficial.

Hypoglycaemic agents
Additive effects are theoretically possible — andrographis has hypoglycaemic activity comparable to that of metformin in vivo. Use together with caution; however, interaction may be beneficial.

Drugs metabolised chiefly via the cytochrome p450 system
It is currently unclear whether there is a significant interaction between andrographis and these medications, as in vivo evidence is suggestive of enzyme induction, but this observation has not yet been investigated in clinical studies (Singh et al 2001). Recently andrographolide was shown to strongly induce the CYP 1A1 induction pathway; however, the clinical significance of this is unknown (Jaruchotikamol et al 2007). Another in vitro study has demonstrated an inhibitive effect of andrographis extract and andrographolide on CYP3A and 2C9 pathways (Pekthong et al 2008). It is recommended that patients be observed to ensure that drug effectiveness is not compromised.

Immunosuppressants
Reduced drug activity is theoretically possible, as immunostimulant activity has been demonstrated in vivo (Puri et al 1993) — use caution in the immunosuppressed.

CONTRAINDICATIONS AND PRECAUTIONS
Suspend use of concentrated extracts 1 week before major surgery.

PREGNANCY USE
Not recommended for use in pregnancy. There is conflicting evidence about the safety of andrographis in pregnancy.

PATIENTS' FAQs
What will this herb do for me?
Andrographis has been traditionally used to improve digestion, as a liver tonic and to fight off infection. Clinical studies confirm that it is an effective symptom reliever for the common cold, uncomplicated URTIs and pharyngotonsillitis. It has also been used to reduce the risk of developing the common cold in winter.
When will it start to work?
During an acute infection, effects may be seen within 3–4 days of starting the correct dose. Used in lower doses for prevention, effects are seen after 3 months' continual use.

Are there any safety issues?

Andrographis is not recommended in pregnancy and may interact with a range of pharmaceutical drugs, so advice from a health professional is required.

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PRACTICE POINTS/PATIENT COUNSELLING

- Several clinical studies suggest that andrographis, both as a stand-alone treatment and in combination with Siberian ginseng, is a useful treatment in cases of common cold, pharyngotonsillitis and uncomplicated URTIs, with significant symptom relief experienced after 3 days' use.
- Clinical studies are lacking, but animal experiments suggest that andrographis may be useful in cases of hepatotoxicity (paracetamol), to reduce myocardial reperfusion injury, improve blood glucose management in diabetes, and in hypertension.
- Traditionally, the herb is used to increase bile production and relieve symptoms of dyspepsia and flatulence, loss of appetite and general debility.
- Because of the extreme bitterness of the herb, solid-dose forms may be better tolerated than liquid preparations.
- Andrographis is not recommended for use in pregnancy.
- There are several theoretical drug interactions with this herb — check interaction data for more details.

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L-Arginine

BACKGROUND AND RELEVANT PHARMACOKINETICS

L-Arginine is a basic, semi-essential amino acid that was discovered in 1886 in lupin seedlings and then in 1895 in mammalian protein (Boger & Bode-Boger 2001). For humans L-arginine is considered to be a semi-essential amino acid or a conditionally essential amino acid, as requirements may increase during metabolic stress or when there is insufficient endogenous L-arginine for optimal growth or tissue repair; for birds and carnivores it is an essential amino acid. It is also the most abundant nitrogen carrier in animals and humans.

Ingested arginine is rapidly cleared from the plasma, and arginine metabolism occurs via a number of pathways although not all pathways are well defined. Arginine is involved in two major metabolic pathways: the nitric oxide synthase (NOS) pathway and the arginase pathway.

In the nitric oxide synthase (NOS) pathway, L-arginine is converted to nitric oxide (NO) and L-citrulline. Three isoforms of NOS (neuronal, inducible and endothelial) have been discovered, each with a different function. Nitric oxide (NO) is a free radical that has vasodilatory and angiogenic characteristics. It regulates nutrient metabolism, plays a role in the circulatory and respiratory systems, especially endothelial function, and exerts numerous other effects in the body.

In the arginase pathway, conversion of L-arginine into L-ornithine and urea is catalysed by the activity of arginase, with the subsequent production of polyamines such as putrescine, spermidine and spermine. Polyamines are essential for cell proliferation and differentiation, tissue growth, and development, and are involved in neurogenesis (Yi et al 2009).

L-Arginine is an essential component in the urea cycle, which is the only pathway in mammals that allows elimination of continuously generated toxic ammonia. Arginine can be synthesised endogenously, mostly in the kidneys and to some degree in liver from the amino acids aspartate and citrulline by arginine synthase.

Arginine is incorporated in the synthesis of proteins, and L-arginine is also required for the production of creatine, which in its phosphorylated form plays an essential role in the energy metabolism of muscle, nerve and testis. Creatine degrades into creatinine, which is removed from the body by the kidneys. Homeostasis of plasma L-arginine is regulated by dietary arginine intake, arginine synthesis, and metabolism and protein turnover.

Ingested arginine is rapidly absorbed and metabolised in the gastrointestinal tract. There is little urinary arginine excretion because it is mostly reabsorbed.

CHEMICAL COMPONENTS

2-amino-5-guanidino-pentanoic acid

FOOD SOURCES

Free arginine is found in dietary protein, commonly in meat, fish, poultry, milk and dairy products, and nuts and seeds (King et al 2008). Other dietary sources include barley, brown rice, buckwheat, chocolate, corn, oats, raisins, and soy. It has been estimated that each gram of dietary protein provides 54 mg of L-arginine, and that 3–6 g of L-arginine is absorbed each day in adults who ingest a normal Western diet (Boger & Bode-Boger 2001, Visek 1986). Dietary lysine competes with arginine for uptake, so low lysine diets are recommended for enhanced arginine absorption (Stargrove et al 2008).

DEFICIENCY SIGNS AND SYMPTOMS

A deficiency of arginine may affect growth and development, insulin production, lipid and protein metabolism, or glucose tolerance. Arginine deficiency may be associated with poor wound healing, hair loss or breakage, liver disease, constipation or skin rash.

MAIN ACTIONS

Arginine is involved in numerous important and diverse biochemical pathways. L-Arginine and its metabolites produce a myriad of effects in the body including pH regulation, depolarisation of endothelial cell membranes, macronutrient metabolism, cell-mediated immunity and antitumour activity, and it is an essential intermediate in the urea cycle (Wahlqvist 2002). L-Arginine also influences the release of such hormones as corticotrophin-releasing factor, insulin, glucagon, prolactin, aldosterone and somatostatin.

Growth hormone and immune function

Arginine triggers the release of growth hormone, which then increases the cytotoxic activity of macrophages, natural killer cells, cytotoxic T cells and neutrophils (Wahlqvist 2002).

Nitric oxide (NO) production

Although the arginine–NO pathway represents only a fraction of the total arginine metabolism, it has attracted considerable interest because of the many roles that NO plays in almost all organ systems. Nitric oxide is a free radical molecule that is synthesised in all mammalian cells from L-arginine by NO synthase (NOS) (Tapiero et al 2002). NO is recognised as an ubiquitous mediator, produced by many cell types, that has diverse and complex actions in multiple organ systems (Rawlingson 2003).

As a precursor of NO, L-arginine influences functions as varied as neurotransmission, vasodilation, inflammation, host defence, cytotoxicity, airway and vascular smooth muscle relaxation, mucociliary clearance and airway mucus secretion, and regulation of gene expression (Chionglo Sy et al 2006).

Cardiovascular disease

Arginine seems to exert its effects in the cardiovascular system mostly through the formation of NO, although it has NO-independent haemodynamic effects as well.

Through NO-dependent actions, arginine can increase smooth-muscle cell relaxation and endothelial cell proliferation, as well as promote angiogenesis and decrease platelet aggregation, leukocyte adhesion, superoxide production, endothelin-1 release and smooth-muscle proliferation (Chionglo Sy et al 2006). NO has also been known as endothelium-derived relaxing factor (EDRF), which is responsible for maintaining vasomotor tone and systemic blood pressure. It also controls intravascular volume by enhancing renin secretion and natriuresis (Rawlingson 2003).

NO-independent actions include: increased plasmin generation or fibrinolysis; augmented release of insulin, growth hormone and glucagon; decreased blood viscosity and formation of fibrin; and decreased angiotensin-converting enzyme activity (Chionglo Sy et al 2006).

CLINICAL USE

Arginine can have one of two forms, the L-form and the D-form, as do most other amino acids. The majority of research literature focuses on oral L-arginine because it has a longer half-life and better long-term effects than systemic forms and would be the preferred route (Blum et al 1999). The role of arginine in NO production has formed the basis of its application in various disease states such as cardiovascular disease, sexual dysfunction, peripheral arterial disease, asthma and interstitial cystitis.

Cardiovascular disease

In the management of cardiovascular disease, arginine supplementation is noted to improve endothelial function, particularly in hypercholesterolaemia and atherosclerosis (Boger & Bode-Boger 2001). Under- or over-production of NO is considered to be a contributing factor to cardiovascular disease, or it may be a consequence of disease, leading to active investigations into the potential for the L-arginine–NO system as a therapeutic target for a variety of conditions such as hypertension, atherosclerosis and ischaemic stroke (Rawlingson 2003).

Numerous animal studies have investigated the effects of L-arginine supplementation on measures of atherosclerotic lesion formation and on several markers of endothelial health and function, such as macrophage function, platelet aggregation and adhesion, and response to injury. L-Arginine supplementation appears to be of benefit regarding many parameters of vascular health: in particular, experimental models indicate slowed progression of the atherosclerotic disease process (Preli et al 2002; Boger & Bode-Boger 2001), although there is controversy as to whether pre-existing lesions are affected by L-arginine supplementation.

Human clinical trials have shown mixed results. A review of oral L-arginine supplementation identified 17 clinical studies that investigated its effects on vascular health (Preli et al 2002). The duration of supplementation varied from 3 days to 6 months, and doses used varied from 6 g to 36 g daily, usually in divided doses. Studies were grouped into those investigating effects on small vessels, large vessels, coronary blood flow, adhesion molecule expression and monocyte adhesion, platelet aggregation and adhesion, limb ischaemia, exercise tolerance and myocardial infarction.

Of the 17 studies reviewed, 12 produced positive results and showed inhibition of platelet aggregation and adhesion, decreased monocyte adhesion resulting in decreased atherogenesis, improved endothelium-dependent vasodilation, or greater pain-free and total walking distance in intermittent claudication. In chronic heart failure patients, improvements in forearm blood flow, walking distance and subjective symptoms were reported. In hypercholesterolaemia, all four studies reviewed produced positive results, suggesting that this subgroup may be particularly responsive to therapy with oral L-arginine. The studies showing favourable effects involved subjects with or at risk of vascular disease, whereas two of the five studies showing no beneficial effect on vascular health were conducted with healthy volunteers who did not have endothelial dysfunction. Overall there are subgroups of patients who may gain vascular health benefits from supplementary arginine, particularly patients with less advanced disease (Boger 2008).

Hyperlipidaemia

Treatment with 9 g arginine daily for 6 months improved endothelial function and patient symptom scores in 26 adults with coronary artery disease (Lerman et al 1998). Similarly in a study of 27 young hypercholesterolaemic adults, improved endothelial dilation was reported as a result of arginine supplementation (21 g/day) for one month (Clarkson et al 1996). Decreased serum total cholesterol levels were reported in a study of 45 healthy elderly adults who were treated with 30 g Arg-aspartate/day (equivalent to 17 g arginine) for 2 weeks (Hurson et al 1995).

Hypertension

Both oral and intravenous administration of L-arginine may reduce blood pressure. Intravenous administration of L-arginine reduces blood pressure in both healthy subjects and in patients with vascular disease. In a randomised, placebo-controlled, crossover study by West et al (2005), the benefit of oral arginine supplementation (12 g per day for 3 weeks) was investigated in 16 middle-aged men with hypercholesterolaemia. In contrast to the results of other studies where arginine was administered intravenously, L-arginine supplementation did not affect lipids, glucose or inflammatory biomarkers; however, there was a reduction in homocysteine and blood pressure.

Myocardial infarction

Some studies have reported that orally administered arginine improves cardiovascular function and reduces myocardial ischaemia in coronary artery disease, whereas others have noted increased

mortality. In a randomised, controlled study by Schulman et al (2006) 153 patients with acute ST-segment elevation myocardial infarcts were given 9 g arginine (as arg-HCL) a day or a placebo for 6 months; however, this study was terminated while in progress, as a significant increase in death rate was noted (8.6% in the group given arg versus zero in the placebo group; $P = 0.01$). The supplementary arginine was implicated by the authors but this assumption was not verified.

In a large, multicentre, randomised, double-blind, placebo-controlled study, 792 patients with coronary artery disease were included within 24 hours of the onset of acute MI; the arginine group received 3 × 3 g L-arginine a day for 1 month. The results showed very little difference between the two groups with respect to various metabolic and clinical markers, although the arginine-supplemented group had favourable trends. However, positive results were seen in a subgroup of patients with hypercholesterolaemia (Bednarz et al 2005).

Angina

Not all studies report efficacy of arginine supplementation for the treatment of angina. A randomised, controlled study of 40 men with stable angina receiving 15 g arginine on a daily basis for 2 weeks did not show benefits for endothelium-dependent vasodilation, oxidative stress or exercise performance (Walker et al 2001). However, in a randomised controlled study 10 patients with stable angina who were given 12 g arginine daily for 6 weeks demonstrated increased exercise tolerance benefits, decreased lactate accumulation and decreased heart rate (Doutreleau et al 2006).

Congestive heart failure

Studies report mixed findings regarding the benefits of supplemental arginine in congestive heart failure, although taking L-arginine orally, in combination with conventional treatment, seems to improve glomerular filtration rate (GFR), creatinine clearance, and sodium and water elimination after saline loading.

A study of 21 patients with congestive heart failure who were given 9 g arginine daily for 7 days reported prolonged exercise capability (Bednarz et al 2004). However, in general, improvements in exercise tolerance, quality of life and peripheral vascular resistance are not consistently obtained. Oral arginine treatment did not have beneficial effects in endothelial function for 20 heart-failure patients who received 20 g per day for 4 weeks (Chin-Dusting et al 1996).

Peripheral arterial disease

Dietary supplementation of L-arginine has been reported to improve endothelium-dependent vasodilation, limb blood flow and walking distance in peripheral arterial disease (PAD). In a recent study (Oka et al 2005), 80 patients with PAD and intermittent claudication were randomly assigned oral doses of L-arginine in 3 g increments up to 9 g daily in three divided doses over a period of 12 weeks. No major differences were noted, although there was a trend for an improvement in walking speed in patients receiving L-arginine, and the group that was treated with 3 g L-arginine daily also demonstrated a moderate improvement in walking distance. On the other hand, in a recent randomised, controlled study of 133 patients with peripheral arterial occlusive disease who received L-arginine supplementation of 3 g daily for 6 months, no benefit was reported regarding vascular function and there was a significant decrease in the absolute walking distance (Wilson et al 2007).

Diabetes

Reduced arginine plasma levels have been noted in patients with diabetes mellitus (DM), and reports indicate that endothelial function may be improved in such patients by supplementary arginine. Arginine may also counteract lipid peroxidation, thus reducing the long-term complications of DM. In a small study of 10 women with type 2 DM, improved endothelial function was noted after they were given 9 g arginine daily for 1 week (Regensteiner et al 2003).

Erectile dysfunction

Supplementary arginine has been investigated for its effect on erectile function, given the role of NO in the corpus cavernosum; the research in this area has mixed findings. In a large prospective randomised, double-blind placebo-controlled study, a high dose of arginine (5 g/d) was administered for 6 weeks to 50 men with organic erectile dysfunction (ED) and significant improvement in sexual function was reported only in men with abnormal nitric oxide metabolism (Chen et al 1999). However, in a randomised, placebo-controlled, crossover oral study of 32 patients with mixed-type impotence who were treated with 3 × 500 mg L-arginine/day for 17 days, the results showed the supplement was no more effective than the placebo (Klotz et al 1999). Taking L-arginine orally in high doses, 5 g daily, seems to improve subjective assessment of sexual function in men with organic ED, but taking lower doses might not be effective. A combination of arginyl aspartate (equivalent to 1.7 g of L-arginine a day) with pycnogenol was administered to 40 men, aged 25–45 years for 3 months; by the third month up to 92% of the men reported improved erectile function without any side effects (Stanislavov & Nikolova 2003).

Chemotherapy adjunct

There are conflicting reports about the value of arginine supplementation during chemotherapy. As some studies have also used other supplementary constituents, it is difficult to attribute any benefits solely to arginine (Appleton 2002). Importantly, arginine has been implicated in promoting cancer growth, since polyamines can act as growth factors for cancers, and this might be of concern in long-term arginine treatment. Precautionary measures regarding L-arginine administration should be considered in cancer patients, although in recent years immunomodulating (IM) formulas containing supplementary

arginine have been used safely (Aiko et al 2008, Marik & Zaloga 2008).

Interstitial cystitis

The results of taking L-arginine for the management of interstitial cystitis (IC) are mixed. In a double-blind placebo-controlled crossover study (Cartledge et al 2000), 16 patients were randomised to receive L-arginine (2.4 g/day) or a placebo for 1 month. Although some patients reported improvement in their symptoms the effects were only small and probably not clinically significant. A randomised, double-blind, placebo-controlled study with 53 patients who received 1500 mg L-arginine or a placebo orally for 3 months reported less pain and urgency in some of the patients (Korting et al 1999). A small study in which patients were treated with either 3 g or 10 g of supplementary arginine did not report any symptom improvements (Ehrén et al 1998). Overall, taking L-arginine orally may reduce symptoms, especially pain associated with interstitial cystitis, in only some patients.

Enhancing immune function

The results of the utility of supplemental arginine in immunonutrition are mixed. Numerous enteral formulas contain additional arginine for use in catabolic conditions and critical illness; most enteral feeds provide about 12–13 g per 1000 kcal.

A recent systematic review investigated the impact in critical illness of IM formulas containing various supplementary nutrients such as arginine (ranging from 6.5 to 15 g arginine/L) and glutamine compared with a control diet. Analysis of 24 studies (3013 patients) found that IM diets with supplementary arginine, with or without various supplementary nutrients, did not result in improved outcomes in intensive care, trauma and burn patients (Marik & Zaloga 2008).

Wound healing

A number of studies have reported that dietary L-arginine supplementation enhances wound healing and immunity. A randomised, controlled study with 29 older adults receiving 15 g arginine daily for 4 weeks reported improved immune function (Moriguti et al 2005). Similarly, improved wound healing was reported in another randomised, controlled study, in which 17 g arginine as arginine-aspartate (30 g/day) was administered daily for 14 days to 30 healthy elderly people (Kirk et al 1993). Improved wound healing was noted in a randomised controlled trial of experimental surgical wounds in 36 healthy adults who were given 17–25 g oral arginine per day (Barbul et al 1990).

Renal failure

There are mixed reports about the benefit of supplemental L-arginine in the management of chronic renal failure. There was no improvement in renal function in a randomised, double-blind, placebo-controlled study of 24 patients who were given 200 mg/kg (14 g/70 kg) arginine daily for 6 months (De Nicola et al 1999). A study of 76 renal transplant patients who were given 9 g arginine a day and canola oil as a source of omega-3 fatty acids for 3 years noted reduced infections and transplant rejections (Alexander et al 2005).

OTHER USES

HIV — general support

Supplementary arginine may have a beneficial role in the care of human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome (AIDS). A few studies have already been conducted investigating the effects of a combination of arginine with vitamins, minerals and glutamine; body weight was reported to increase, but other findings were mixed (Appleton 2002).

Asthma

Arginine supplementation may be beneficial to patients with asthma, although there are reports that such supplementation may also cause exacerbation of airway inflammation (Coman et al 2008). At present, it is unclear whether L-arginine supplementation results in any clinically significant benefit to patients with asthma.

Cystic fibrosis

In a small, double-blind, placebo-controlled crossover study of 10 patients with cystic fibrosis, arginine supplementation of 200 mg/kg administered for 6 weeks resulted in increased NO production (Grasemann et al 2005).

Dementia

Increased cognitive function and reduced lipid peroxidation was noted in 16 elderly patients with senile dementia who were administered arginine (1.6 g/day) (Ohtsuka & Nakaya 2000).

Subfertility

It has been well documented that arginine-deficient diets in adult men result in markedly decreased sperm counts. Infertile men given 500 mg arginine-HCL per day for 6–8 weeks were reported to have increased sperm counts, although such supplementation had no effect if the baseline sperm counts were less than 10 million/mL (Appleton 2002). Results of a single study note that supplementation of 16 g of arginine per day improved ovarian response and pregnancy rate in poor responders to 'in vitro fertilisation' (Battaglia et al 1999).

DOSAGE RANGE

General guide

- Overall L-arginine is well tolerated in doses < 30 g administered orally, intravenously or via the intra-arterial route (Boger & Bode-Boger 2001). It is best taken in divided doses to improve overall absorption, reaching 1.5–6 g daily.
- In a recent risk assessment by Shao and Hancock (2008) the following recommendations have been made: NOAEL and LOAEL >42 g/day l-arginine; observed safe level (OSL) 20 g/day. ULS 20 g/day.

According to clinical studies

- Angina pectoris: oral 12 g/day (uncertain efficacy).
- Coronary artery disease: 9 g/day.
- Erectile dysfunction: 5 g/day (in men with abnormal NO metabolism).
- Hyperlipidaemia: 30 g/day (uncertain efficacy).
- Wound healing: 17 g/day.

TOXICITY

Overall, arginine administration is considered safe for humans and animals (Wu & Meininger 2000). However, it must be noted that vasodilation and hypotension can result from the overproduction of NO due to excess administration of arginine.

ADVERSE REACTIONS

L-Arginine supplementation has been used safely and has been associated with only minor side effects in clinical studies lasting from a few days to months (Shao & Hathcock 2008). Orally, L-arginine can cause abdominal pain and bloating, diarrhoea and gout. Gastrointestinal disturbances have been reported as a result of arginine supplementation, although the studies have been of a mixed nature and involved a range of patients (Grimble 2007) whereas these effects have not been reported in controlled studies.

There has been only limited consideration of safety aspects of supplemental arginine, even though numerous animal studies have been conducted examining a wide range of diseases (Shao & Hathcock 2008). In humans only one study has used a high oral arginine dose of 42 g on a daily basis without any adverse effects being noted (Shao & Hathcock 2008).

SIGNIFICANT INTERACTIONS

No controlled studies are available to determine the significance of the proposed interactions, so they remain speculative.

Antihypertensive medicines

Theoretically, additive hypotensive effects may occur — use with caution. Potential benefits under professional supervision.

Nitrates

Theoretically, additive vasodilation and hypotensive effects may occur — use with caution.

L-Lysine

A limited number of research studies report that high doses of arginine could be unfavourable, as arginine may compete with lysine uptake by tissues; caution is needed if considering the administration of both amino acids, since supplemental arginine has been reported to affect proliferation of the herpes simplex virus (Griffith et al 1981).

Sildenafil

Theoretically, additive vasodilation and hypotensive effects may occur — use with caution. Potential benefits under supervision.

CONTRAINDICATIONS AND PRECAUTIONS

Intravenous arginine needs to be administered with care, as overdose may result in adverse consequences such as severe hyponatraemia (Shao & Hathcock 2008), and high doses with high osmolality can cause local irritation and phlebitis (Boger & Bode-Boger 2001).

Other side effects that can occur as a result of administering arginine are metabolic acidosis associated with arrhythmias, and hyperkalaemia and increases in blood nitrogen urea in patients with liver disease and/or renal impairment (Boger & Bode-Boger 2001).

Hyperkalaemia and hypophosphataemia in patients with diabetes has also been reported (Boger & Bode-Boger 2001). Supplementary arginine may also be contraindicated in patients with systemic septic shock and hypotension due to NO production (Feihl et al 2001).

Caution is necessary in using high doses of 30 g/d in cancer patients, as even short-term use for 3 days may be linked to increased tumour growth.

PREGNANCY USE

At present there is insufficient reliable information available about the safety of L-arginine during pregnancy and for nursing mothers. Dietary intake levels are likely to be safe.

PRACTICE POINTS/PATIENT COUNSELLING

- L-Arginine is a conditionally essential amino acid for humans; requirements may be increased during metabolic stress or when there is insufficient endogenous L-arginine for optimal growth or tissue repair.
- Arginine deficiency can affect growth and development, insulin production, lipid and protein metabolism, and glucose tolerance. Clinical symptoms include poor wound healing, hair loss or breakage, liver disease, constipation and skin rashes.
- The role of arginine in NO production forms the basis of its application in cardiovascular disease, peripheral arterial disease, sexual dysfunction, asthma and interstitial cystitis.
- Oral arginine supplementation shows promise in the treatment of angina, hyperlipidaemia, congestive heart failure, improving vascular health (reducing atherogenesis) and interstitial cystitis; however, results are not consistent.
- Oral arginine supplementation has shown benefits in erectile dysfunction and promoting wound healing
- Arginine supplementation should be used with caution in people with cancer, kidney and/or liver impairment, schizophrenia, herpes simplex virus or a history of myocardial infarction.

PATIENTS' FAQs

What will this supplement do for me?

Arginine supplementation is used in cardiovascular disease, peripheral arterial disease, sexual dysfunction, wound healing and several other conditions. Its effects will depend on the dose used and indication for use.

When will it start to work?

This depends on the dose used and indication for use.

Are there any safety issues?

Arginine supplementation should be used with caution in people with cancer, kidney and/or liver impairment, schizophrenia, herpes simplex virus or a history of myocardial infarction. There are also several drug interactions that should be considered before use.

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Astragalus

HISTORICAL NOTE Astragalus was first recorded in *Shen Nong's Materia Medica* about two thousand years ago and was believed to stimulate immune function, have antioxidant effects and other benefits in the treatment of viral infections and cardiovascular disease (Zhang et al 2007). The roots of astragalus are still considered among the most important and popular Chinese herbs for invigorating vital energy, health promotion and strengthening Qi. Western herbalists began using astragalus in the 1800s in various tonics and the gummy sap (tragacanth) is still used as an emulsifier, food thickener and antidiarrhoeal agent. Today, Western herbalists use astragalus as an immunomodulating agent, adaptogen and in the management of cardiovascular disease.

COMMON NAME
Astragalus

OTHER NAMES
Astragali, beg kei, bei qi, hwanggi, huang-qi, milk vetch, goat's horn, green dragon, Mongolian milk, ogi, Syrian tragacanth

BOTANICAL NAME/FAMILY
Astragalus membranaceus (family Fabaceae)

PLANT PART USED
Root

CHEMICAL COMPONENTS
Astragalus is a chemically complex herb and contains over 60 components including beta-sitosterol, glycosides (astragalosides I through VII, soyasaponin, daucosterin), polysaccharides (astroglucans A through C), saponins such as cycloastragenol, astragalosides, isoflavones and other flavonoids, plant acid, choline, betaine, rumatakenin, formonetin, amino acids (including gamma-aminobutyric acid) and various microelements (Duke 2003, Li & Wang 2005, Mills & Bone 2000).

MAIN ACTIONS
Evidence about mechanisms of action is mainly derived from in vitro and animal studies.

Immune modulation
Studies using various experimental models indicate that astragalus has immune-modulating activity. Astragalus stimulates macrophage activity and enhances antibody responses (Chu et al 1988, Jin et al 1994, Sugiura et al 1993). Astragalus enhances lymphocyte blastogenesis in vitro (Sun et al 1983). Immunostimulant effects have also been observed in the presence of immunosuppressive therapy in vivo (Jin et al 1999).

Although usually administered in the oral form, research has also been undertaken with injectable forms. A study conducted with both normal and immunosuppressed mice found that astragalus administration increased antibody responses and T helper cell activity (Zhao et al 1990). A flavonoid identified in the stem and leaves of astragalus is believed to be one of the main constituents responsible for immune modulation (Jiao et al 1999) and more recently, several studies have identified that astragalus polysaccharide (APS) also exerts significant biological effects, including increasing cellular and humoral immune responses in vivo (Guo et al 2004).

Studies in animal models have found APS stimulates B cells and macrophage activity, but not T cells (Shao et al 2004). More specifically, APS stimulates macrophages to produce nitric oxide (NO) through induction of NO synthase transcription leading to increased macrophage cytolytic function (Lee & Jeon 2005). Other in vitro and animal studies reveal that APS increases beneficial gut flora and decreases harmful gut bacteria, suggesting beneficial immune effects within the gastrointestinal tract (Guo et al 2003).

Cardiovascular effects
The effect of astragalus on heart function has been the subject of several investigations and, most recently, a Cochrane Systematic Review, which analysed studies of Chinese herbs used in viral myocarditis and concluded that astragalus significantly improves

Clinical note — Polysaccharides and immunity
One of the most promising recent alternatives to antibiotic treatment is the use of immunomodulators for enhancing host defence responses. Several types of immunomodulators have been identified, most recently botanically sourced polysaccharides isolated from mushrooms, algae, lichens and higher plants. These polysaccharides tend to have a broad spectrum of therapeutic properties and relatively low toxicity. One of the primary mechanisms responsible for immunomodulation involves non-specific induction of the immune system, which is thought to occur via macrophage stimulation and modulation of the complement system. According to one report, polysaccharides isolated from 35 plant species among 20 different families have been shown to increase macrophage cytotoxic activity against tumour cells and microorganisms, activate phagocytic activity, increase reactive oxygen species (ROS) and nitric oxide (NO) production, and enhance secretion of cytokines and chemokines, such as TNF-alpha, IL-1beta, IL-6, IL-8, IL-12, IFN-gamma and IFN-beta2 (Schepetkin & Quinn 2006). These effects have a major influence on the body's ability to respond rapidly and potently to a diverse array of pathogens, giving the polysaccharides wide clinical application.

cardiac function, arrhythmia and creatinine kinase levels (Liu, Yang & Du 2004). The review assessed data from 10 randomised clinical trials that used a single preparation of astragalus and one that used a combination containing mainly astragalus; however, the authors stated that the trials had poor quality in terms of design, reporting and methodology.

Several constituents from *Astragalus* spp. have demonstrated effects on heart contractility, heart rate and blood pressure. In particular, 3-nitropropionic acid (NPA) has been shown to decrease blood pressure and induce bradycardia when administered as an IV preparation in normotensive rats or renal hypertensive dogs (Castillo et al 1993). Another compound, astragaloside IV, demonstrated positive inotropic activity in patients with congestive heart failure (Luo et al 1995).

Recent research indicates that astragalus improves endothelial function by increasing the bioavailability of NO and decreasing reactive oxygen species production (Zhang et al 2007).

Antioxidant

In vivo studies have found that astragalus raises superoxide dismutase activity in the brain and liver, thus demonstrating an indirect antioxidant activity (Jin et al 1999). The constituent astragaloside IV (20 and 40 mg/kg) prevented the formation of cerebral infarction after induced focal ischaemia in an animal model, most likely due to its antioxidant and anti-inflammatory actions (Luo et al 2004).

Anticarcinogenic effects

Both in vitro and animal studies indicate that astragalus may have a role as adjunctive therapy in the treatment of some cancers. In vivo studies have shown that astragalus extract exerts anticarcinogenic effects in carcinogen-treated mice, mediated through activation of cytotoxic activity and the production of cytokines (Kurashige et al 1999). An extract of the root (90 and 180 mg/kg) prevented the development of preneoplastic lesions and delayed hepatic cancer in chemically-induced hepatocarcinogenesis in a rat model (Cui et al 2003). The saponin, astragaloside IV, can increase the fibrinolytic potential of cultured human umbilical vein endothelial cells by downregulating the expression of plasminogen activator inhibitor type 1 (Zhang et al 1997). Another constituent (astragalan) increased the secretion of TNF-alpha and TNF-beta (Zhao & Kong 1993).

An animal study using a combination of *Astragalus membranaceus* and *Ligustrum lucidum* demonstrated antitumour effects by augmenting phagocyte and lymphokine-activated killer cell activities (Lau et al 1994).

Digestive effects

Astragalus strengthens the movement and muscle tone of the small intestine (especially the jejunum) in animal tests, which may account for its clinical application in a variety of common digestive symptoms (Yang 1993).

Improved sperm motility

An aqueous extract of *Astragalus membranaceus* was tested in vitro and found to have a significant stimulatory effect on sperm motility (Hong et al 1992). Astragalus has shown a significant effect on human sperm motility in vitro when compared with controls (Liu et al 2004).

Hepatoprotective actions

Astragalus has hepatoprotective qualities against paracetamol, carbon tetrachloride and D-galactosamine poisoning (Zhang et al 1990). Increases in liver glutathione levels observed as a result of the herbal treatment may be partly responsible. Studies have identified the constituent betaine as an important contributor to this activity.

OTHER ACTIONS

Astragalus is also thought to have adaptogenic activity. It has shown weak oestrogenic activity in vitro when compared with other Chinese herbs and controls (17-beta-oestradiol) (Zhang et al 2005). This could partially explain its traditional use in menopause.

CLINICAL USE

Astragalus is a popular Chinese herbal medicine and has been the subject of many clinical trials, mainly published in foreign language peer-reviewed journals. To provide a more complete description of the evidence available, secondary sources have been used when necessary. As a reflection of clinical practice, astragalus is sometimes tested in combination with other herbal medicines, and such instances are stated as such in this review.

Viral infection

Owing to its immunomodulatary actions, astragalus is widely used for preventing and treating various viral infections. A popular use is as a preventive treatment against common colds and influenza. To date, scientific evidence is scant to confirm effectiveness, although one review stated that astragalus has been tested in clinical trials in China, reducing the incidence and shortening the duration of the common cold (Murray 1995).

Viral myocarditis

Astragalus has been investigated in viral myocarditis in several clinical studies. It was found to significantly improve cardiac function, arrhythmia and creatinine kinase levels according to a Cochrane review of randomised trials (Liu, Yang & Du 2004). Although this result is encouraging, the authors noted that trials were generally of poor quality in terms of design, reporting and methodology. Despite these limitations, the studies identified activity on heart contractility, heart rate and blood pressure for several constituents in astragalus, providing support for clinical observations. Recent research showed that astragalus also improves endothelial function, achieved by increasing the bioavailability of NO and decreasing reactive oxygen species production (Zhang et al 2007).

Several in vivo and in vitro studies have found some antagonistic effects on the enterovirus coxsackie B and a reduction in myocardial injury (Lu et al 1999, Peng et al 1995, Rui et al 1993, Yang et al 1990), thought to be due to the astragalosides in the herb (Lu et al 1999).

Cardiovascular disease

Congestive heart failure

Some of the clinical signs and symptoms recognised as indicators for this medicine by TCM practitioners suggest that the herb may be useful for congestive heart failure. Recent positive results obtained in clinical studies have reinforced this possibility.

The two clinical trials investigated continuous intravenous administration of astragalus. One study involving 19 patients found that after 2 weeks continuous administration of astragaloside IV, major symptoms were alleviated in 15 patients. Treatment produced a positive inotropic effect, improved left ventricular modelling and ejection function (Luo et al 1995).

The second study, involving 38 patients with congestive heart failure who were administered astragalus 24 g intravenously for 2 weeks, found that 13.6% had significantly shortened ventricular late potentials (Shi et al 1991).

Angina pectoris

Two clinical studies have suggested that astragalus may be an effective treatment for angina pectoris. One study used Doppler echocardiography to study the action of astragalus on left ventricular function in 20 patients with angina pectoris. Treatment resulted in increased cardiac output after 2 weeks, but no improvement in left ventricular diastolic function (Lei et al 1994). One Chinese study reported 92 patients with ischaemic heart disease who were successfully treated with astragalus as measured by electrocardiogram readings. Results obtained with the herb were considered superior to those obtained with nifedipine (Li et al 1995).

Cancer

Astragalus is used in cancer patients to enhance the effectiveness of chemotherapy and reduce associated side-effects. It is additionally used to enhance immune function.

Few details are available of clinical studies looking at the potential for astragalus to alter patient survival outcomes, as most information has been published in non-English journals. However, two clinical studies are worth mentioning which suggest that intravenously administered astragalus may have potential benefit as adjunctive therapy when given with chemotherapy. One randomised study of 120 cancer patients receiving chemotherapy administered IV astragalus extract daily (20 mL in 250 mL normal saline), which slowed tumour growth compared to controls (Duan & Wang 2002). Four treatment cycles were administered lasting 21 days each. Unfortunately, no further details are available about this study.

Another randomised study investigated IV astragalus in 60 patients with advanced non-small cell lung cancer (Zou & Liu 2003). This time 2–3 treatment cycles were given of 21–18 days each. The mean remission rate was 5.4 months in the herbal treated group versus 3.3 months in the untreated group, and the 1 year survival rate was 46.75% with herbal treatment versus 30.0% without. All differences were considered statistically significant. Once again further details are not available in English.

Colorectal cancer

According to a 2005 Cochrane systematic review, astragalus may be a useful adjunct to chemotherapy in colorectal cancer as it reduces treatment side effects. The review assessed various Chinese herbal medicines taken in combination with chemotherapy for colorectal cancer for their ability to reduce common side effects of chemotherapy such as nausea, vomiting, sore mouth, diarrhoea, hepatotoxicity, myelosuppression and immunosuppression (Taixiang et al 2005). Four trials were analysed: adjunctive treatment with astragalus was compared with chemotherapy alone in three trials, and with two other Chinese herbal treatments in the fourth trial. Overall, herbal treatment resulted in a significant reduction in the proportion of patients who experienced nausea and vomiting when decoctions of huang-qi (astragalus) compounds were given in addition to chemotherapy. There was also a decrease in the rate of leucopenia (WBC $< 3 \times 10^9$/L) and increased proportions of T-lymphocyte subsets: CD3, CD4 and CD8 with no significant effects on immunoglobulins G, A or M. The authors concluded that astragalus may stimulate immunocompetent cells and decrease chemotherapy side effects, however a definitive conclusion could not be made because of the studies' methodological limitations. Additionally, no evidence of harm was identified with use of the Chinese herbal treatment in these studies.

Reducing adverse effects of treatment (in combination)

Zee-Cheng screened and evaluated 116 Kampo formulas and identified 15 that potentiated therapeutic effects, reduced the adverse toxicity of various anticancer drugs, and exhibited immune-modulating effects in cancer patients. Among these, shi-quan-da-bu-tang (SQT) was selected as the most effective and studied further. SQT is a popular TCM herbal combination consisting of 10 medicinal herbs, including *Astragalus membranaceus*. Using both animal models and clinical studies, the herbal combination produced several promising results (Zee-Cheng 1992).

Prostate cancer (in combination)

Although no human studies could be located, encouraging results were obtained from an in vitro study investigating the effects of a proprietary product known as Equiguard™ on prostate cancer cells. It is prepared according to TCM principles and contains standardised extracts of nine herbs: herba epimedium brevicornum maxim (stem and leaves), radix morindae officinalis (root), fructus rosae laevigatae michx (fruit), rubus chingii hu (fruit), *Schisandra chinensis* (Turz.) Baill (fruit), *Ligustrum lucidum* Ait (fruit), *Cuscuta chinensis* Lam (seed), *Psoralea corylifolia* L. (fruit), and *Astragalus membranaceus* (root). It is used in TCM to restore Qi in the urogenital region. The product was shown to significantly reduce cancer cell growth, induce apoptosis, suppress expression of the androgen receptor and lower intracellular and secreted prostate-specific antigen (Hsieh et al 2002).

Clinical note — The concept of an adaptogen is foreign to Western medicine but often used in traditional medicine

The term 'adaptogen' was first coined by N. Lazarev in the Soviet Union in the mid-20th century, although the concept has been used for centuries in traditional herbal systems. Adaptogens are considered natural bioregulators that increase the ability of the organism to adapt to environmental factors and to avoid damage from such factors. Herbal medicines with adaptogenic activity are used when extremes of physical or emotional activity are present, environmental influences are severe, or allostatic load has developed over time. The aim of treatment is to improve the patient's endurance and ability to deal with these changes in a healthy way, and for abnormal parameters to shift towards normal. The best-known example of a plant adaptogen is ginseng (*Panax ginseng*), but others are also well established such as *Schisandra chinensis*, *Eleutherococcus senticosus* (Siberian ginseng), *Astragalus membranaceus* and *Withania somnifera* (see also Siberian ginseng and Glossary).

Chronic kidney disease

Astragalus is one of the most commonly prescribed Chinese herbs in chronic kidney disease (CKD). Pharmacological studies have confirmed that different constituents in the herb have effects which could be valuable in CKD such as anti-oxidant, diuretic and anti-inflammatory effects, and studies in rat models indicate that astragalus decreases glomerular hyperperfusion and improves kidney function (Li & Wang 2005). A meta-analysis of 14 randomised controlled trials involving 524 Chinese patients with primary nephrotic syndrome showed that treatment with astragalus for 1 to 3 months could increase the therapeutic effect of prednisone and immunosuppressants (reported in Li & Wang 2005). Herbal treatment decreased proteinuria and increased levels of total cholesterol and albumin. Although further details are unavailable, these results are encouraging.

OTHER USES

Traditional uses

Within traditional Chinese herbal medicine, astragalus is used to invigorate and tonify Qi and the blood, as an adaptogen, for severe blood loss, fatigue, anorexia, organ prolapse, chronic diarrhoea, shortness of breath, sweating and to enhance recuperation (Mills & Bone 2000).

Cholesterol reduction (in combination with other herbs)

A randomised, double-blind clinical trial compared the effects of a traditional Chinese herbal medicine combination known as jian yan ling (which includes astragalus as a main ingredient) to a placebo in 128 hyperlipidaemic patients. After 3 months' treatment it was found that total cholesterol, triglyceride, apoproteins and lipoprotein-a levels were significantly reduced in the treatment group, compared with a placebo (Lu et al 1994).

Asthma (in combination with other herbs)

A herbal combination of *Astragalus membranaceus, Codonopsis pilulosa* and *Glycyrrhiza uralensis* was investigated in an open study for effects on airway responsiveness. Twenty-eight patients with asthma were treated with the herbal combination for 6 weeks, after which values for FVC, FEV_1 and PEF were all higher than at baseline (Wang et al 1998).

Memory deficits (in combination with other herbs)

In TCM, invigorating Qi and warming Yang are believed to have a beneficial therapeutic effect on some brain diseases, such as senile dementia. Some studies have been conducted to determine the outcome of following this ancient principle.

A decoction of astragalus produced neuroprotective effects in rats with experimentally induced cerebral ischaemia (Quan & Du 1998), and memory enhancement has been observed in vivo (Jin et al 1999).

One article reports on 100 cases of children with minimal brain dysfunction and compared the effects of a TCM combination (*Bupleurum chinense*, *Scutellaria baicalensis*, *Astragalus membranaceus*, *Codonopsis pilulosa*, *Ligustrum lucidum*, *Lophatherum gracile* and thread of ivory) to the Western medical approach (methylphenidate (Ritalin™) 5–15 mg/day). A collation of results found that the herbal treatment produced a clinically effective rate of 87.5% compared with 90% in the Ritalin group, with the herbal treatment group reporting fewer side-effects (Zhang & Huang 1990).

DOSAGE RANGE

- Dried root: 2–30 g/day.
- Liquid extract (1:2) or solid dose equivalent: 4.5–8.5 mL/day.
- Decoction: 8–12 g divided into two doses daily on an empty stomach.

TOXICITY

Animal studies have shown that the herb has a wide safety margin.

ADVERSE REACTIONS

None known.

SIGNIFICANT INTERACTIONS

Interactions are theoretical and based on the herb's pharmacodynamic effects, therefore clinical significance is unclear and remains to be confirmed.

Acyclovir

Possibly enhances antiviral activity against herpes simplex type 1 (Stargrove et al 2008) — adjunctive use may be beneficial.

Immunosuppressant medication

Reduced drug activity is theoretically possible, as immunostimulant activity has been demonstrated — use caution.

Positive inotropic drugs

Additive effects are theoretically possible with intravenous administration of astragalus, based on positive inotropic activity identified in clinical studies. The clinical significance of these findings for oral dose forms is unknown — observe patients using high-dose astragalus preparations.

Cyclophosphamide

Adjunctive treatment with astragalus may have beneficial effects in regards to improving patient well-being and reducing adverse effects associated with treatment such as nausea and vomiting — only use combination under professional supervision.

CONTRAINDICATIONS AND PRECAUTIONS

According to the principles of TCM, astragalus should not be used during the acute stages of an infection.

PREGNANCY USE

Safety is unknown although no evidence of fetal damage has been reported in animal studies (Mills & Bone 2005).

PRACTICE POINTS/PATIENT COUNSELLING

- Astragalus is widely used as an immunostimulant medicine to reduce the incidence of the common cold and influenza and is sometimes used to improve immune responses to other viral infections such as herpes simplex type 1.
- It is also used to enhance recuperation and reduce fatigue, and reduce the side effects of chemotherapy whilst improving immune function.
- Astragalus is a commonly prescribed Chinese herb in chronic kidney disease.
- According to TCM practice it is widely used to invigorate and tonify Qi and the blood, and as an important adaptogen.
- Some evidence suggests it enhances digestion, improves heart function in viral myocarditis, and may improve sperm counts and have hepatoprotective activity.
- Under the TCM system of use, astragalus is not used during periods of acute infection.
- In clinical practice it is often used in combination with other herbs such as *Bupleurum chinense*, *Scutellaria baicalensis* and *Codonopsis pilulosa*. As such, most clinical trials have tested combination formulas.

PATIENTS' FAQs

What will this herb do for me?

Astragalus appears to have numerous biological effects, such as digestive and immune system stimulation and heart muscle stimulation. Early research suggests that it may have a role in the treatment of asthma, memory deficits, elevated cholesterol levels and as an adjunct to chemotherapy treatment for cancer.

When will it start working?

This will depend on the indication and dose; some studies have shown that effects can begin within 2 weeks.

Are there any safety issues?

Overall the herb appears to be safe, although it has the potential to interact with some medicines. Professional supervision is advised for people receiving chemotherapy and considering using this herb.

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Baical skullcap

HISTORICAL NOTE Baical skullcap is a TCM herb used to clear 'heat and dry dampness'. Diseases with heat are associated with symptoms such as fever, irritability, thirst, cough and expectoration of thick, yellow sputum. Damp diseases may be associated with diarrhoea, a feeling of heaviness of the chest and painful urination (Bensky & Gamble 1986). From a modern perspective this suggests that baical may be useful for infection and inflammation of the respiratory, digestive and urinary systems. Scientific investigations have indeed shown that baical skullcap and its constituents have antibacterial, antiviral, anti-inflammatory, hepatoprotective and diuretic actions (Zhang et al 2001).

OTHER NAMES

Baical skullcap, Chinese skullcap, huang qin (Mandarin), ogon (Japanese), scute

BOTANICAL NAME/FAMILY

Scutellaria baicalensis Georgi (family Lamiaceae)

PLANT PART USED

Root

CHEMICAL COMPONENTS

Baical skullcap contains numerous flavonoids and their glycosides. The main flavonoids are baicalin and its aglycone, baicalein, and wogonin. Resin and tannins are also present.

Baical also contains melatonin. It has been shown that dietary melatonin directly contributes to the circulating level of the hormone. The clinical effects of plant-derived melatonin remains to be investigated (Hardeland & Poeggeler 2003). Baicalin itself is poorly absorbed from the gut, but is hydrolysed to its aglycone, baicalein, by intestinal bacteria and then restored to its original form from the absorbed baicalein in the body (Akao et al 2000).

MAIN ACTIONS

The actions of baical skullcap, some of its individual constituents, and combination formulations have been studied in various models.

Anti-inflammatory

The anti-inflammatory activity of baical skullcap has been well documented by in vitro and in vivo studies. The main constituents responsible are baicalein and wogonin (Chang et al 2001, Chi et al 2001, Chung et al 1995, Huang et al 2006, Krakauer et al 2001, Li et al 2000a, Park et al 2001, Wakabayashi 1999).

In a study using mice, baicalein 50 mg/kg has been shown to ameliorate the inflammatory symptoms of induced colitis, including body weight loss, blood haemoglobin content, rectal bleeding and other histological and biochemical parameters (Hong et al 2002). Pretreatment with wogonin also significantly reduced ethanol-induced gastric damage in vivo (Park et al 2004) and reduced immunoglobulin E, IL-4, IL-5 and IL-10 secretion in a colitis-induced mouse model (Lim 2004). The methanolic extract of the baical skullcap root and its flavonoids wogonin, baicalein and baicalin have been shown to inhibit lipopolysaccharide-induced inflammation of the gingivae (gums) in vivo. The three flavonoids exerted an anti-inflammatory effect similar to prednisolone. In addition, the flavonoids exerted a moderate inhibition (33–36%) of collagenolytic activity, comparable to the 40% inhibition by tetracycline. Meanwhile, the cellular activity of fibroblasts was augmented remarkably (40%) by baicalein and slightly by baicalin and wogonin. Consistent with the cellular activation, the flavonoids enhanced the synthesis of both collagen and total protein in fibroblasts in vitro (Chung et al 1995).

The anti-inflammatory mechanisms are varied and summarised below.

Chemokine binding

It has been proposed that the anti-inflammatory activity is partly caused by limiting the biological function of chemokines.

Excessive release of pro-inflammatory cytokines mediates the toxic effect of superantigenic staphylococcal exotoxins. In vitro data suggest that baicalin may be therapeutically useful for mitigating the pathogenic effects of staphylococcal exotoxins by inhibiting the signalling pathways activated by superantigens (Krakauer et al 2001).

Baicalin inhibited the binding of a number of chemokines to human leukocytes or cells expressing specific chemokine receptors, with an associated reduced capacity of the chemokines to induce cell migration. Based on these results, it is possible that the anti-inflammatory mechanism of baicalin is to bind a variety of chemokines and limit their biological function (Bao et al 2000, Li et al 2000a).

Four major flavonoids from baical have been shown in vitro to suppress eotaxin. Eotaxin is an eosinophil-specific chemokine associated with the recruitment of eosinophils to sites of allergic inflammation. Eotaxin is produced by IL-4 plus TNF-alpha-stimulated human fibroblasts. This may explain why it has been used traditionally in the treatment of bronchial asthma (Nakajima et al 2001). Various flavonoids, including wogonin and baicalein, have been shown to inhibit chemically induced histamine release from rat mast cells in vitro (Kubo et al 1984).

COX-2 inhibition

Wogonin is a direct COX-2 inhibitor. Wogonin inhibits both inducible nitric oxide synthase and cyclo-oxygenase 2 induction (Chen et al 2001 & 2008, Chi et al 2001, Wakabayashi & Yasui 2000). Wogonin has been shown to inhibit inducible PGE_2 production in macrophages by inhibiting COX-2 (Wakabayashi & Yasui 2000). Additionally baicalein, but not baicalin, has been shown to inhibit COX-2 expression in lipopolysaccharide induced RAW 264.7 cells (a murine leukaemic macrophage-like cell line) (Woo et al 2006). Both compounds also suppressed inducible NO synthase (iNOS) protein expression, iNOS mRNA expression, and NO production in a dose-dependent manner.

Wogonin may be beneficial for COX-2-related skin disorders. When applied topically to the dorsal skin of mice, it inhibited COX-2 expression and PGE_2 production (Byoung et al 2001, Chi et al 2003, Park et al 2001).

Lipoxygenase inhibition

The inhibition of the 5-lipoxygenase pathway of arachidonic acid metabolism may be one of the mechanisms of baicalein's anti-inflammatory activity according to an in vivo study (Butenko et al 1993).

Nitric oxide synthase inhibition

Baicalein and wogonin attenuate lipopolysaccharide-stimulated nitric oxide synthase induction in macrophages, which helps to explain the anti-inflammatory action of these flavonoid compounds (Cheng et al 2007, Wakabayashi 1999).

Antioxidant activity

The anti-inflammatory activity of baicalein may be associated with inhibition of leukocyte adhesion by the scavenging of reactive oxygen intermediates (Shen et al 2003).

Nuclear factor kappa B inhibition

Baicalin has been shown to inhibit nuclear factor kappa B (NFkB) in vitro (Cheng et al 2007, Hsieh et al 2007, Kim et al 2006, Wang et al 2006).

Antifibrotic

A methanolic extract of baical skullcap has been shown to inhibit fibrosis and lipid peroxidation induced by bile duct ligation or carbon tetrachloride in rat liver. Bile duct ligation in rodents is an experimental model for extrahepatic cholestasis caused by, for example, cholelithiasis (gall stones). Liver fibrosis was assessed by histological observation and by measuring levels of liver hydroxyproline, lipid peroxidation based on malondialdehyde production, and serum enzyme activities. Treatment with baical skullcap significantly reduced the levels of liver hydroxyproline and malondialdehyde, with improved histological findings (Nan et al 2002).

Hepatoprotective

Baicalein, baicalin and wogonin have been shown to have hepatoprotective effects in vivo. The flavonoids decrease the toxicity produced by a variety of chemicals. Significant protective effects were seen by comparing the serum levels of AST and ALT and by histopathologic examination (Lin & Shieh 1996). Two different dried root preparations of baical skullcap (1% of total feed) were added to the diet of animals that were subsequently exposed to aflatoxin-B1 (de Boer et al 2005). Mix A contained 3.13 microgram/g baicalin, 1.5 microgram/g baicalein, 0.021 microgram/g wogonin and 65.3 nmol/g melatonin compared to 0.94 microgram/g baicalin, 0.41 microgram/g baicalein, and 0.003 microgram/g wogonin and 1176 nmol/g melatonin in mix B. The addition of mix A and B reduced hepatic damage by approximately 60 and 77%, respectively. The feed mixtures also increased the expression of the gene for glutathione S-transferase A5 by 2.5 to 3.0-fold. Interestingly the mix with the lower concentration of flavonoids was the more protective. The authors explain this by stating that it was probably due to the much higher (18-fold) amount of melatonin which has been shown to enhance aflatoxin detoxification pathways in animals.

Baicalein, baicalin and wogonin have also been shown to inhibit hemin-nitrite-H_2O_2 induced liver injury in a dose-dependent manner by inhibiting oxidation and nitration (Zhao et al 2006). In other in vitro and in vivo studies baicalin reduced tert-butyl hydroperoxide hepatic damage, attenuated glutathione depletion, ALT and AST levels and reduced oxidative stress (Hwang et al 2005). Additionally, further histopathological examination showed a significant reduction in the incidence of hepatic lesions and swelling.

In combination

The combination Sho-saiko-to (a Japanese herbal supplement containing baical skullcap, also known as Minor Bupleurum Combination and Xiao Chai Hu Tang in Mandarin) has been shown to inhibit chemical hepatocarcinogenesis in animals, act as a biological response modifier and suppress the proliferation of hepatoma cells by inducing apoptosis and arresting the cell cycle. These effects may be due to baicalin, baicalein and saikosaponins (from *Bupleurum falcatum*), which have the ability to inhibit cell proliferation (Shimizu 2000). Further testing is required to determine the role of baical skullcap in achieving these effects.

Antioxidant

Several studies have shown baical skullcap constituents to be antioxidant in vitro and in vivo. Flavones produced a concentration-dependent protection of liposome membrane against UV-induced oxidation. The ability to scavenge free radicals and protect against the effects of lipid peroxidation (in this case caused by sunlight irradiation) may in part account for the herb's underlying mechanism of action (Gabrielska et al 1997).

Fourteen flavonoids and flavone glycosides have been demonstrated to possess good free radical scavenging properties in vitro (Gao et al 1999, Lin & Shieh 1996). Baicalin has been found to have the most potent antioxidant effect (Bochorakova et al 2003).

Baicalin's antioxidant effect is based on scavenging superoxide radicals, whereas baicalein is a good xanthine oxidase inhibitor. Xanthine oxidase inhibitors are known to be therapeutically useful for the treatment of hepatitis and brain tumours (Gao et al 2001).

Oxidative stress plays an important role in the pathological process of neurodegenerative diseases including Alzheimer's disease. The protective effects of baical flavonoids on the oxidative injury of neuronal cells have been demonstrated in vitro (Choi et al 2002, Gao et al 2001).

Anti-allergic

Flavonoids have anti-allergic activities and are known to inhibit histamine release from basophils and mast cells. Luteolin and baicalein have been shown to inhibit IgE antibody-mediated immediate and late phase allergic reactions in mice. In an in-vitro study, luteolin and baicalein inhibited IgE-mediated histamine release from mast cells. The compounds also inhibited IgE-mediated TNF-alpha and IL-6 production from mast cells. However, the compounds did not affect the histamine, serotonin or platelet-activating factor-induced cutaneous reactions in rats (Kimata et al 2000). Wogonin, wogonoside and 3,5,7,2',6'-pentahydroxyl flavanone isolated from baical skullcap decrease histamine, leukotriene B4 and IgE in vitro (Lim 2004).

Baicalein is 5–10-fold more potent than the anti-allergic drug azelastine. Baicalein significantly suppressed leukotriene C4 release by polymorphonuclear leukocytes obtained from asthmatic patients compared with healthy subjects (Niitsuma et al 2001).

Neuroprotective

Many in vitro and in vivo trials have demonstrated the neuroprotective effects of flavonoids derived from baical skullcap (Cho & Lee 2004, Heo et al 2004, Piao et al 2004, Shang et al 2006a, Son et al 2004).

Cerebral ischaemia can cause a significant elevation in the concentrations of amino acid neurotransmitters in the cerebral cortex. Baicalin administration can attenuate the elevations of glutamic acid and aspartic acid induced by cerebral ischaemia. This research demonstrates that baicalin may act as a neuroprotectant during cerebral ischaemia. Wogonin has been shown to exert a neuroprotective effect by inhibiting microglial activation, which is a critical component of pathogenic inflammatory responses in neurodegenerative diseases. Wogonin inhibited inflammatory activation of cultured brain microglia by diminishing lipopolysaccharide-induced TNF-alpha, IL-1-beta and NO production. Wogonin inhibited NO production by suppressing iNOS induction and NF-kappa-B activation in microglia. The neuroprotective effect of wogonin has also been shown in vivo using two experimental brain injury models (Lee et al 2003).

An in vivo study in rats induced with permanent global ischaemia demonstrated that daily oral doses of baical skullcap flavonoids (35 mg/kg) for 19–20 days statistically increased learning and memory ability and attenuated neural injury (Shang et al 2005). A follow-up in vivo study demonstrated that the flavonoid fraction also reduced neural damage and memory deficits after permanent cerebral ischaemia (Shang et al 2006b).

Another in vivo study investigated the neuroprotective effects of baicalein in a Parkinsonian experimental model and demonstrated improved motor coordination and a reduction in spontaneous motor activity (Cheng et al 2008). This was thought to be the result of increased dopamine and serotonin levels in the striatum, leading to increased dopaminergic neurons and an inhibition of oxidative stress. Baical skullcap is used in TCM for the treatment of stroke. Methanol extracts from the dried roots (0.1–10 mg/kg IP) significantly protected neurons against 10 min transient forebrain ischaemia. The extract inhibited microglial TNF-alpha and NO production, and protected cells from hydrogen peroxide-induced toxicity in vitro (Kim et al 2001).

Hypotensive

Treatment with baicalein lowered blood pressure in hypertensive but not in normotensive rats according to one study (Takizawa et al 1998). Baical extract and baicalein have also been shown to lower blood pressure in rats and cats (Kaye et al 1997, Takizawa et al 1998). The exact mechanisms underlying the hypotensive action are unclear. One in vivo study has shown that *Scutellaria baicalensis* extract produces peripheral vasodilatation (Lin et al 1980). A 2005 review concluded that baical skullcap is effective for renin-dependent hypertension and that in vivo effects may be due to the inhibition of lipoxygenase, reducing the production and release of arachidonic-acid derived vasoconstrictor substances (Huang et al 2005).

Vascular activity

Monocyte chemotactic protein-1 (MCP-1), a potent chemoattractant for monocytes, plays a crucial role in cases of early inflammatory responses, including atherosclerosis. Wogonin has been shown to inhibit MCP-1 induction by endothelial cells in a dose-dependent manner. Wogonin and baical skullcap may be potentially beneficial in inflammatory and vascular disorders (Chang et al 2001). Baicalein significantly suppressed intimal hyperplasia and cell proliferation in a vascular injury study in vivo (Peng et al 2008).

Antiplatelet

Baical flavonoids have been shown to inhibit platelet aggregation in vitro (Kubo et al 1985). Baicalein inhibited the elevation of calcium induced by thrombin and thrombin receptor agonist peptide. These findings suggest a potential benefit of baicalein in the treatment of arteriosclerosis and thrombosis (Kimura et al 1997).

Cholesterol reduction

Flavonoids are known to reduce cholesterol. A 30-day study of induced hyperlipidaemia in rats found that baicalein, quercetin, rutin and naringin reduced cholesterol, with baicalein the most potent. Baicalein was also the most effective flavonoid in reducing triglyceride levels (De Oliveira et al 2002). In another in vivo study, rats were fed a cholesterol-laden diet and half were also given *S. baicalensis* radix extract (Regulska-Ilow et al 2004). The treatment rats displayed a significant reduction in plasma triglycerides and total cholesterol compared with control animals. The mechanism may be due to the increased activity of lecithin cholesterol acyltransferase (You et al 2008).

Anxiolytic

Wogonin, baicalein, scutellarein and baicalin (in reducing order of potency), which all contain a certain flavonoid phenylbenzopyrone nucleus, have been shown in vitro to bind with the benzodiazepine site of the GABA-A receptor (Hui et al 2000).

Oral administration of wogonin (7.5–30 mg/kg) has been shown to interact with GABA-A receptors and produce an anxiolytic response that was similar to diazepam in the elevated plus-maze. Unlike benzodiazepines, wogonin was able to reduce anxiety without causing sedation or myorelaxation (Hui et al 2002, Kwok et al 2002).

Baicalin (10 mg/kg IP) and baicalin (20 mg/kg IP) have also been shown in vivo to produce an anxiolytic effect, mediated through activation of the benzodiazepine binding sites of GABA-A receptors (Liao et al 2003).

Two other flavones, 5,7-dihydroxy-6-methoxyflavone (oroxylin A) and 5,7,2'-trihydroxy-6,8-dimethoxyflavone (K36), also act as antagonists at the GABA-A recognition site and have demonstrated anxiolytic activity in vivo (Huen et al 2003a, b).

A water-extract of baical skullcap demonstrated anticonvulsant activity against electroshock-induced tonic seizures in vivo. Interestingly, the authors suggest that the effect might not be via the activation of the benzodiazepine binding site of GABA-A receptors, but probably via the prevention of seizure spread (Liao et al 2003, Wang et al 2000). A more recent study has shown that wogonin has anticonvulsive effects mediated by GABA (Park et al 2007).

Antimicrobial

Numerous studies have found that baical extract and flavonoids exert antibacterial, antiviral and antifungal actions. The antimicrobial effect of baical extract is mild and the clinical efficacy of baical in infectious diseases may be more associated with its anti-inflammatory rather than its antimicrobial activities.

Antibacterial

Baical skullcap decoction was investigated for bacteriostatic and bactericidal activity against a selection of oral bacteria, including suspected periodontopathogens. At a concentration of 2%, the decoction was bacteriostatic for 8 of 11 bacteria tested, but a

concentration of 3.13% or greater was required for bactericidal effect (Tsao et al 1982).

Baical aqueous-extract, but not its flavonoids, baicalin and baicalein, demonstrated antibacterial effects against the enteric pathogen *Salmonella typhimurium*. The effect was compatible with commercial antibiotics including ampicillin, chloramphenicol, and streptomycin. In contrast, the growth of a non-pathogenic *Escherichia coli* strain was unaffected by baical (Hahm et al 2001). One study demonstrated that the addition of baical skullcap in vitro improved the responsiveness of antibiotics for the treatment of MRSA (Yang et al 2005).

Baicalin has been shown to reduce the pathogenic effects of superantigenic staphylococcal exotoxins by inhibiting the signalling pathways activated by superantigens (Krakauer et al 2001).

Antiviral

Antiviral effects have been demonstrated for baical in numerous in vitro and in vivo tests. Baical extract significantly inhibits hepatitis C RNA replication in vivo (Tang et al 2003) and in vitro studies have found that:

- Intraperitoneal and intranasal administration of baical flavonoids significantly inhibits influenza virus in vivo and in vitro (Nagai et al 1989, 1992a, 1992b, 1995a, 1995b).
- Baicalein inhibits HIV-1 infection at the level of viral entry (a process known to involve interaction between HIV-1 envelope proteins and the cellular CD4 and chemokine receptors) (Li et al 2000b).
- Baicalin inhibits human T-cell leukaemia virus type I (HTLV-I) (Baylor et al 1992).
- Aqueous extract inhibits HIV type-1 protease (Lam et al 2000).
- Baicalin inhibits HIV-1 infection and replication (Li et al 1993).
- Baical flavonoids inhibit Epstein-Barr virus early antigen activation (Konoshima et al 1992).
- Wogonin suppresses hepatitis B virus surface antigen production without evidence of cytotoxicity (Huang et al 2000).
- 5,7,4'-trihydroxy-8-methoxyflavone inhibits the fusion of influenza virus with endosome/lysosome membrane (Nagai et al 1995a).
- Virus replication is suppressed, partly by inhibiting the fusion of viral envelopes with the endosome/lysosome membrane which occurs at the early stage of the virus infection cycle (Nagai et al 1995b).
- The flavones in baical have potent influenza virus sialidase inhibitory activity and anti-influenza virus activity in vivo (Nagai et al 1992b).
- Baicalin may selectively induce apoptosis of HIV-infected human T-leukaemia (CEM-HIV) cells, which have a high virus-releasing capacity, and stimulate proliferation of CEM-HIV cells, which have a relatively lower capacity of HIV-production (Wu et al 1995).

Antifungal

Antifungal activity has been demonstrated by several studies (Blaszczyk et al 2000, Yang et al 1995). Baical extract showed clear fungistatic activities in vitro against some cutaneous and unusual pathogenic fungi, and particularly against strains of *Candida albicans*, *Cryptococcus neoformans* and *Pityrosporum ovale*. The antifungal substance was isolated and found to be baicalein (Yang et al 1995). Of 56 Chinese antimicrobial plants, baical root extract had the highest activity against *C. albicans* (Blaszczyk et al 2000).

Anti-ulcerogenic

Extracts prepared from grass and roots of *S. baicalensis* showed high anti-ulcerogenic activity in vivo (Amosova et al 1998).

Antidiabetic

5-alpha-aldose inhibition

Diabetic patients may accumulate intracellular quantities of the sugars sorbitol and dulcitol, because of an increase in the polyol pathway involving the enzyme 5-alpha-aldose. Oral baicalin and liquid extract of licorice (also rich in flavonoids) reduced the sorbitol levels in the red blood cells of diabetic rats (Lin et al 1980, Zhou & Zhang 1989).

Alpha-glucosidase inhibition

Alpha-glucosidase inhibitors (e.g. acarbose) are a class of oral medicine for type 2 diabetes, which blocks the enzymes that digest starches in food. The result is a slower and lower rise in blood glucose throughout the day, especially immediately after meals. Methanol extracts of *S. baicalensis*, *Rheum officinale* and *Paeonia suffruticosa* showed potent inhibitory activity against rat intestinal sucrase. The active principles were identified as baicalein and methyl gallate (from the latter two plants). In addition to its activity against the rat enzyme, baicalein also inhibited human intestinal sucrase in vitro (Nishioka et al 1998).

Anti-emetic

Pretreatment with baical root extract has been shown to decrease cisplatin-induced pica in rats (animal models use the level of kaolin [type of clay] intake as a measure of the intensity of nausea). This suggests that baical may help to reduce cisplatin-induced nausea and emesis during cancer therapy (Aung et al 2003, Mehendale et al 2004, Wu et al 1995), although clinical testing is required to confirm significance.

Two in vivo trials found that *S. baicalensis* significantly attenuated ritonavir-induced pica, and demonstrated possible efficacy for the management of ritonavir-induced nausea in HIV treatment (Aung et al 2005, Mehendale et al 2007).

Renal–urinary tract activity

Baicalein inhibited angiotensin II-induced increases in the cellular protein content of aortic smooth muscle cells in vitro (Natarajan et al 1994). In another in vitro study, baicalein prevented the angiotensin II-induced increase in renal vascular resistance by 50% and promoted glomerular filtration rate (Bell-Quilley et al 1993). Pretreatment with baicalein significantly inhibited a decrease in nephrotoxin-induced

glomerular filtration rate and renal blood flow in vivo (Wu et al 1993). Oral intake of baical flavonoids and extract has been shown to produce a diuretic effect.

Anticancer

Immunostimulation (in combination)

Sho-saiko-to has been shown to stimulate granulocyte colony-stimulating factor (G-CSF), which may explain its use in infectious diseases and cancer (Yamashiki et al 1992). Like growth hormone, IL-2 and -4 and interferon, G-CSF is a signalling ligand that stimulates immune function. G-CSF, a glycoprotein produced mainly by macrophages, induces proliferation of neutrophil colonies and differentiation of precursor cells to neutrophils. It also stimulates the activity of mature neutrophils (Hill et al 1993).

Sho-saiko-to is known to significantly suppress cancer development in the liver. Moderate regulation of the cytokine production system in patients with hepatitis C by using Sho-saiko-to may be useful in the prevention of disease progression (Yamashiki et al 1997). One possible mechanism for the beneficial effects of this formula in patients with liver cirrhosis may be the improvement in production of IL-12, which is an important cytokine for maintenance of normal systemic defence and bioregulation. This effect of Sho-saiko-to is attributed to two of its seven herb components, baical and licorice root (Yamashiki et al 1999).

Patients who were given baical skullcap showed a tendency towards an increase in the relative number of T-lymphocytes and their theophylline-resistant population during antitumour chemotherapy. The immunoregulation index in this case was approximately twice the background value during the period of investigation. The inclusion of baical skullcap in the therapeutic complex promoted an increase in the number of immunoglobulins A at a stable level of IgG (Smolianinov et al 1997).

Apoptosis induction

Baicalein, baicalin and wogonin have been shown to induce apoptosis, disrupt the mitochondria and inhibit proliferation in various human hepatoma cell lines (Chang et al 2002, Chen et al 2000). The platelet-type 12-lipoxygenase (12-LOX) pathway is a critical regulator of prostate cancer progression and apoptosis by affecting various proteins regulating these processes. Baicalein inhibits 12-LOX and may be a potential therapeutic agent in the treatment of prostate cancer (Pidgeon et al 2002) as well as breast cancer (Tong et al 2002) and lung cancer (Leung et al 2007).

Antiproliferative

Baicalein, baicalin and wogonin have been shown to induce apoptosis and inhibit proliferation in various human hepatoma cell lines (Chang et al 2002).

Baicalin has been shown to inhibit the proliferation of prostate cancer cells in vitro. However, the response to baicalin differed among different cell lines (Chan et al 2000).

COX-2, which converts arachidonic acid to PGE_2, is highly expressed in head and neck squamous cell carcinoma (HNSCC). *S. baicalensis*, but not baicalein, suppressed proliferation, cell nuclear antigen expression and PGE_2 synthesis. A 66% reduction in tumour mass was observed in the mice with HNSCC. Baical selectively and effectively inhibits cancer cell growth in vitro and in vivo and can be an effective chemotherapeutic agent for HNSCC (Zhang et al 2003).

In a study designed to determine the ability of baical skullcap to inhibit various human cancer cells in vitro, *S. baicalensis* demonstrated a significant dose-dependent, growth inhibition on squamous cell carcinoma, breast cancer, hepatocellular carcinoma, prostate carcinoma and colon cancer cell lines (Ye et al 2002). Prostate and breast cancer cells were particularly sensitive. Baical skullcap has also been shown to arrest mouse leukaemia cell proliferation in vivo (Ciesielska et al 2002, 2004). Inhibition of PGE_2 synthesis via suppression of COX-2 expression may be responsible for its anticancer activity (Ye et al 2002). Differences in the biological effects of baical compared with baicalein suggest synergistic effects among components in baical (Zhang et al 2003). Another study has shown complete inhibition of acute lymphatic leukaemia, myeloma and lymphoma cell lines in vitro (Kumagai et al 2007). Baicalein, baicalin and wogonin have been shown to reduce proliferation of human bladder cancer cell lines in a dose-dependent manner, but baicalin exhibited the greatest antiproliferative activity. In an in vivo study baical skullcap extract had a significant inhibition of tumour growth ($P < 0.05$) (Ikemoto et al 2000).

Baical skullcap significantly inhibited prostate-specific antigen production and reduced PGE_2 synthesis via direct inhibition of COX-2 activity in vitro (Ye et al 2007). The extract also reduced cyclin D1, resulting in a G1 phase arrest, and inhibited cyclin-dependent kinase 1 (cdk1) expression and kinase activity leading to a G2/M cell cycle arrest. An animal study reported a 50% reduction in tumour volume after 7 weeks (Ye et al 2007). Another study found that baicalein, wogonin, neobaicalein and skullcap-flavone inhibited prostate cancer cell proliferation in vitro (Bonham et al 2005). Additionally, the in vivo phase of the study found that baicalein (20 mg/kg/day) reduced the growth of prostate cancer xenografts in mice by 55% after 2 weeks.

Wogonin inhibited PMA-induced COX-2 protein and mRNA levels in human lung epithelial cancer cells (Chen et al 2008). It appears that this was due to activator protein 1 (AP1) inhibition.

Adjunct to chemotherapy

In experiments with murine and rat transplantable tumours, baical skullcap extract treatment improved cyclophosphamide and 5-fluorouracil-induced myelotoxicity and decreased tumour cell viability

(Razina et al 1987). Wogonin has also demonstrated the ability to hasten etoposide-induced apoptotic cell death (Lee et al 2007). Another in vitro study found that wogonin increased apoptosis and induced cell cycle arrest at the G2/M phase (Himeji et al 2007).

Prevention of metastases

The advancement of Pliss' lymphosarcoma in rats is associated with disorders of platelet-mediated haemostasis, presenting with either lowered or increased aggregation activity of platelets. Extract of baical was shown to produce a normalising effect on platelet-mediated haemostasis whatever the pattern of alteration. This activity is thought to be important for antitumour and, particularly, metastasis-preventing effects (Razina et al 1989).

Experiments in mice inoculated with metastasising Lewis lung carcinoma showed that the antitumour and antimetastatic effects of cyclophosphamide are potentiated by baical, rose root (*Rhodiola rosea*), licorice (*Glycyrrhiza glabra*), and their principal acting components, baicalin, paratyrosol and glycyrrhizin (Razina et al 2000).

Chemoprevention

Baicalein prevents chemically-induced DNA damage in a cell culture model (Chan et al 2002).

Anti-angiogenesis

Baicalein and baicalin have demonstrated anticancer activity against several cancers in vitro. The flavonoids have also been shown to be potent inhibitors of angiogenesis in vitro and in vivo. Baicalein was found to be more potent than baicalin (Liu et al 2003).

Cytochrome Inhibition

Baical flavonoids inhibit hepatic cytochromes CYP1A2 and CYP3A2 in vitro and in vivo (Kim et al 2002, de Boer et al 2005).

CLINICAL USE

Baical skullcap is an ingredient in the very popular traditional Chinese/Japanese formulation, Minor Bupleurum Combination, also known as Xiao Chai Hu Tang (Chinese) and Sho-saiko-to (Japanese). Minor Bupleurum Combination has been used in China for about 3000 years for the treatment of pyretic diseases.

Minor Bupleurum Combination (Sho-saiko-to) is now a prescription drug approved by the Ministry of Health and Welfare of Japan and widely used in the treatment of chronic viral liver diseases. Since 1999, Sho-saiko-to has been administered to 1.5 million patients with chronic liver diseases, because it can significantly suppress cancer development in the liver (Yamashiki et al 1999). Sho-saiko-to is also used for the treatment of bronchial asthma in Japan (Nakajima et al 2001). As such, many studies have been conducted with the herbal combination making it difficult to determine the role of baical skullcap as a stand-alone treatment.

Minor Bupleurum Combination (Sho-saiko-to, Xiao Chai Hu Tang)

- *Bupleurum falcatum* (bupleurum)
- *Scutellaria baicalensis* (baical skullcap)
- *Pinellia ternata* (pinellia)
- Panax ginseng (Korean ginseng)
- *Zizyphus jujuba* (zizyphus)
- *Glycyrrhiza uralensis* (Chinese licorice)
- *Zingiber officinale* (ginger)

Respiratory infection

Sixty patients with respiratory infection (mainly nosocomial pneumonia) were treated either by injection of baical compound or piperacillin sodium (IV). The total efficacy was evaluated after treatment for 1 week.

- Total effective treatment rates were 73.3% for baical compared with 76.7% in the antibiotic treatment group.
- Body temperature was decreased similarly and symptoms disappeared or were relieved in 11.67 ± 6.75 days with the herb and 11.53 ± 7.30 days with the antibiotic.
- In the piperacillin sodium group, fungal infections occurred in 4 of 30 patients, but there were none in the baical treatment group (Lu 1990).

Bone marrow stimulation during chemotherapy

Haemopoiesis was studied in 88 patients with lung cancer during combination treatment with chemotherapy and a *S. baicalensis* extract. Administration of the plant preparation was associated with haemopoiesis stimulation, intensification of bone marrow erythrocytopoiesis and granulocytopoiesis, and increased numbers of circulating precursors of erythroid and granulomonocytic colony-forming units (Goldberg et al 1997).

Epilepsy (in combination with other herbs)

Saiko-keishi-to, a spray-dried decoction of bupleurum (cinnamon, peony, ginger, licorice, ginseng, pinellia, zizyphus and baical) was administered to 24 people with epilepsy who had frequent uncontrollable seizures (3–5 seizures per day in the most severe case and 5 seizures per month in the mildest case) of various types, despite treatment with pharmaceutical anticonvulsants. Of them, 6 were well controlled with Saiko-keishi-to whereas 13 experienced improvement and 3 showed no effect. No patients experienced worsening of their condition. Two patients dropped out during treatment (Narita et al 1982).

Chronic active hepatitis (in combination with other herbs)

In a double-blind, multicentre clinical study of 222 patients with chronic active hepatitis, Sho-saiko-to was found to significantly decrease AST and ALT values compared with placebo. The difference between the treatment and placebo groups in the mean value was significant after 12 weeks. In patients with chronic active hepatitis type B (HB), a tendency towards a decrease of HB e antigen and an increase of

anti-HB e antibodies was also observed. No remarkable side effects were noticed (Hirayama et al 1989).

Liver fibrosis (in combination with other herbs)

Minor Bupleurum Combination (Sho-saiko-to) has been shown to play a chemopreventive role in the development of hepatocellular carcinoma in cirrhotic patients in a prospective study, and several studies have demonstrated the preventive and therapeutic effects of Sho-saiko-to on experimental hepatic fibrosis (Shimizu 2000). Sho-saiko-to has been shown to inhibit the activation of hepatic stellate cells, the major collagen-producing cells. Sho-saiko-to has a potent antifibrotic effect by inhibiting oxidative stress in hepatocytes and hepatic stellate cells. It is proposed that the active components are baicalin and baicalein, because they both have chemical structures very similar to silybinin, the active compound in *Silybum marianum* (St Mary's thistle), which exhibits antifibrotic activities.

OTHER USES

Because of its wide range of pharmacological effects, baical skullcap is used for many different indications. Although controlled trials are not yet available to determine its effectiveness, evidence from in vitro and animal studies provides a theoretical basis for the following uses:

- chronic inflammatory conditions such as asthma, arthritis and allergies (anti-allergic and anti-inflammatory effects)
- hepatitis (as a hepatoprotective agent)
- common infections such as the common cold (antimicrobial and immunostimulant effects)
- nausea and vomiting (anti-emetic effect)
- mild hypertension (hypotensive activity demonstrated in several animal models).

In practice, baical skullcap is used in combination with other herbs for these conditions.

DOSAGE RANGE

- Dried herb: 6–15 g/day (Bensky & Gamble 1986).
- Liquid extract (1:2): 30–60 mL/week or 4.5–8.5 mL/day in divided doses.

ADVERSE REACTIONS

There have been several case reports of Sho-saiko-to-induced interstitial pneumonia (Liu et al 2002). One case of Sho-saiko-to-induced pneumonia in a patient with autoimmune hepatitis was reported (Katou et al 1999); however, direct toxicity is very low.

Toxicity studies of three different traditional Chinese/Japanese formulations containing baical suggest a very low acute or subchronic toxicity for the herbs in them. The studies found no herb-related abnormalities such as changes in body weight or food consumption, abnormalities on ophthalmological and haematological examination, urinalysis and gross pathological examination, changes in organ weights or optical microscopic examination (Iijima et al 1995, Kanitani et al 1995, Kobayashi et al 1995, Minematsu et al 1992, 1995). The acute lethal activity of wogonin is low, with an LD_{50} of 3.9 g/kg (Kwok et al 2002).

SIGNIFICANT INTERACTIONS

There are reports of baical flavonoids interacting with P450 enzymes. Baical flavonoids inhibit hepatic CYP1A2 (Kim et al 2002) and CYP2E1 expression (Jang et al 2003). Theoretically, inhibition of CYP1A2 and CYP2E1 may affect certain medical drugs metabolised by these P450 enzymes. There are, however, no clinical reports of such herb–drug interactions.

Sho-saiko-to during interferon therapy

Sho-saiko-to, as well as interferon, is used for the treatment of chronic hepatitis. There have been reports of acute pneumonitis due to a possible interferon–herb interaction. Pneumonitis, also called extrinsic allergic alveolitis, is a complex syndrome caused by sensitisation to an allergen. The mechanism of the Sho-saiko-to–interferon interaction seems to be due to an allergic–immunological mechanism rather than direct toxicity (Ishizaki et al 1996) — contraindicated.

Cyclosporin

A decoction of *S. baicalensis* has been reported to significantly decrease plasma levels of cyclosporin in rats. The co-administration of these two substances should be avoided until further research is available (Lai et al 2004).

Warfarin/anticoagulants

Increased risk of bleeding is theoretically possible — use with caution.

CONTRAINDICATIONS AND PRECAUTIONS

Baical skullcap and the formulation Sho-saiko-to (Minor Bupleurum Combination, Xiao Chai Hu Tang) are contraindicated during interferon therapy. Baical is contraindicated in cold conditions in TCM.

PREGNANCY USE

Baical is used in TCM for restless fetus (threatened abortion) and toxaemia of pregnancy. A recent animal study found that baical skullcap combined with *Atractylodes macrocephala* had an anti-abortive effect through inhibition of maternal–fetal interface immunity. The herbs prevented lipopolysaccharide-induced abortion by reducing natural killer cells and interleukin 2 activity (Zhong et al 2002). Although this is encouraging, safety in pregnancy is still unknown.

PATIENTS' FAQs

What can this herb do for me?

Baical skullcap may be useful as an adjunctive therapy during cancer treatment to reduce nausea and immune suppression. Baical skullcap may also be beneficial in the treatment of vascular disorders, allergies, liver disease and infections, hypertension and arthritis; however, effectiveness is largely unknown.

When will it start to work?

For acute allergic and infectious conditions, the beneficial effects of baical skullcap should be noticeable within a few days. For chronic diseases, long-term use is recommended.

Are there any safety issues?

Baical skullcap is a safe and non-toxic herb, which is used in both acute and chronic conditions. It should only be used during pregnancy on the recommendation of a healthcare practitioner. Baical and the formulation Sho-saiko-to (Minor Bupleurum Combination known as Xiao Chai Hu Tang in Mandarin) are contraindicated during interferon therapy.

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PRACTICE POINTS/PATIENT COUNSELLING

- Baical skullcap is a traditional Chinese herb used to treat fever, cough with thick yellow sputum, thirst and irritability, nausea, jaundice and diarrhoea.
- Baical skullcap extract, many of its constituents, and as part of herbal combination treatments, has been studied in many different experimental models. However, few clinical trials have been conducted using baical as a stand-alone treatment.
- It is used to treat chronic inflammatory conditions such as asthma, arthritis and allergy, because of its anti-inflammatory and anti-allergic effects.
- It is used as a hepatoprotective agent in the treatment of hepatitis.
- Because of its antimicrobial and immunostimulant effects, baical is used to treat infections such as the common cold and bronchitis.
- Anti-emetic effects suggest a role in nausea and vomiting.
- Hypotensive activity demonstrated in various animal models provides a basis for its use in hypertension.
- In practice, it is combined with other herbal medicines for a more targeted approach.

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Beta-carotene

BACKGROUND AND RELEVANT PHARMACOKINETICS

Carotenoids

The carotenoids are a family of bright yellow, orange and red compounds found in fruit, vegetables and some animal products such as salmon, lobster and egg yolk. Carotenoids can be divided into the provitamin A group, such as beta-carotene, and xanthophylls such as lutein, zeaxanthin and lycopene, which are important fat-soluble antioxidants. Of the 600 or so carotenoids known to exist in nature, approximately 20 are found in humans. In plants, carotenoids play a vital role in photosynthesis and participate in the energy-transfer process, as well as protecting plants from oxidative damage. The red, orange and yellow colours of these compounds is due to their preferential absorption of blue light, which is the most energetic and hence the most biologically damaging part of the visible spectrum.

In animals, carotenoids have many functions. In addition to providing direct photoprotection via absorption of blue light, carotenoids act as powerful fat-soluble antioxidants linked to oxidation prevention. They also play a role in cellular communication, including stimulation of gap-junction communication which is important for cancer prevention, by regulating cell growth, differentiation, apoptosis and angiogenesis. Carotenoids may also be involved in detoxification of carcinogens, DNA repair and immunosurveillance. These properties are believed to contribute to their antioxidant, immune-enhancing, anticarcinogenic and photoprotective activity.

Beta-carotene was the first of the carotenoids to be discovered, being initially isolated from carrots. The bioavailability of beta-carotene is dependent on its source. In raw foods such as carrots it forms part of a protein-polysaccharide matrix, and absorption is only about 20% of absorption from supplemental forms. Although beta-carotene is lipid soluble, its absorption requires only a limited amount of fat (Roodenburg et al 2000); however, there is a wide individual variation in serum response to beta-carotene administration (Bowen et al 1993, Pryor et al 2000).

Although it has been suggested that different carotenoids compete for absorption, this was not confirmed by a postprandial study (Tyssandier et al 2002). Beta-carotene is absorbed in the intestine and released into the lymphatic circulation within chylomicrons. It is then taken up by hepatocytes and released into the blood, and transported predominantly within LDLs. It is distributed to adipose tissue and the skin and excreted in the faeces (Micromedex 2003). The time to reach peak concentration is up to 4–6 weeks with oral dosing (Mathews-Roth 1990a).

Animal feeding studies suggest that a natural algae-derived beta-carotene isomer mixture is more readily absorbed than synthetic all-*trans* beta-carotene, and that this higher bioavailability can be enhanced by increasing dietary lipid levels (Mokady & Ben-Amotz 1991). Natural algal beta-carotene has also been shown to have higher accumulation in rat liver than synthetic all-*trans* beta-carotene (Ben-Amotz et al 1989, Takenaka et al 1993) with at least a 10-fold higher accumulation having been observed in chick and rat liver (Ben-Amotz et al 1989).

Animal studies suggest that there is some bioconversion within the body between different stereoisomers of beta-carotene (Ben-Amotz et al 2005). Further studies in humans suggest that, regardless of the isomer mix, there is preferential absorption or transport of the all-*trans* isomer in comparison with the 9-*cis* isomer, with plasma levels of the all-*trans* isomer being around 10 times that of the 9-*cis* form (Gaziano et al 1995b, Jensen 1987, Morinobu et al 1994, Stahl & Sies 1993, Tamai et al 1993).

It is suggested that *Helicobacter pylori* infection may impair the protective role of alpha-tocopherol and beta-carotene in the stomach, because infected people have been found to have reduced beta-carotene concentrations in gastric juice, and the presence of gastric atrophy and intestinal metaplasia is associated with reduced mucosal alpha-tocopherol and beta-carotene concentrations (Zhang et al 2000).

Chemical components

Beta-carotene comes in natural and synthetic forms. The natural form is derived mainly from algal sources and consists of roughly equal amount of 9-*cis* and all-*trans* isomers, with small amounts of the 13-*cis* isomer. Synthetic beta-carotene is primarily composed of the all-*trans* isomer, with small residues of the 13-*cis* isomer (PDRHealth 2005). Although all-*trans* beta-carotene is converted into vitamin A, which plays an essential role in vision, growth, reproduction, immune function and maintenance of the skin and mucous membranes (see Vitamin A monograph), the 9-*cis* isomer is not converted into vitamin A but does act as a powerful antioxidant (Ben-Amotz & Levy 1996).

Food sources

Carrots are the major contributors of beta-carotene in the diet, but it is also found in rockmelon, broccoli and spinach. Carotenoids have emerged as the best single tissue marker for a diet rich in fruits and vegetables, and measurements of plasma and tissue carotenoids have an important role in defining the optimal diets for humans (Handelman 2001).

Natural beta-carotene for use in supplements is generally obtained from palm oil or the micromarine algae (phytoplankton) *Dunaliella salina* (also known as *D. bardawil*), which is the richest natural source of beta-carotene. Whole dried *D. salina* is also available in a supplemental form that contains between 1% and 2% beta-carotene. The typical Western diet is estimated to provide approximately 2–4 mg/day of beta-carotene (Pryor et al 2000).

Deficiency signs and symptoms

Beta-carotene is considered a conditionally essential nutrient and becomes an essential nutrient when the dietary intake of retinol (vitamin A) is inadequate.

Low serum beta-carotene levels have been associated with male gender, younger age, lower non-HDL-cholesterol, greater ethanol consumption and higher BMI (Brady et al 1996), insulin resistance (Arnlöv et al 2009), increased lipoprotein density and the presence of inflammation (Kritchevsky 1999), high C-reactive protein (Erlinger et al 2001, Wang et al 2008), high blood glucose (Abahusain et al 1999), hypertension (Coudray et al 1997), exposure to environmental tobacco smoke (Farchi et al 2001), as well as all measures of obesity (Wallstrom et al 2001), including obesity in children (Strauss 1999).

Low serum beta-carotene and/or low beta-carotene intake has also been associated with a number of clinical conditions, such as breast cancer (Hacisevki et al 2003), non-melanoma and melanoma skin cancer (Gollnick & Siebenwirth 2002), rheumatoid arthritis (Kacsur et al 2002), Alzheimer's dementia (Jimenez-Jimenez et al 1999), age-related macular degeneration (Cooper et al 1999a), metabolic syndrome (Revett 2008, Sugiura et al 2008), poor glycaemic control and type 2 diabetes (Abahusain et al 1999, Arnlöv et al 2009, Coudray et al 1997). It has been further shown that the inverse association between serum carotenoid and metabolic syndrome is more evident in current smokers (Revett 2008; Sugiura et al 2008).

Low serum beta-carotene has been independently associated with an increased all-cause mortality risk in older men. Apparently, a synergistic effect occurs between low beta-carotene and high inflammation burden in predicting higher mortality rates (Hu et al 2004). In another study of 668 hospitalised patients aged 70 years or over and 104 healthy controls, the diseased elderly people had reduced plasma levels of retinol, beta-carotene and alpha-tocopherol (Tebi et al 2000). It is unclear whether these observed low levels of beta-carotene seen in disease states are a cause or a result of disease processes.

MAIN ACTIONS

Pro-vitamin A

Beta-carotene is converted to retinoic acid (vitamin A — see Vitamin A monograph) by an enzyme found in the intestinal mucosa and liver, with 2 μg of all-*trans* carotene being equal to 1 μg of all-*trans* retinol (vitamin A) or 3.33 IU (PDRHealth 2005). This conversion is regulated by vitamin A status and may be enhanced by alpha-tocopherol (Wang & Krinsky 1998). Zinc may also be important for bioconversion, as indicated by a double-blind, placebo-controlled trial of 170 pregnant women that found that supplementation zinc improved the postpartum vitamin A status of both mothers and infants (Dijkhuizen et al 2004).

Immunomodulation

The mechanisms by which beta-carotene influences immune function are not well understood, and both direct and indirect effects on immune function, via its pro-vitamin A activity, have been demonstrated (Watson et al 1991). Beta-carotene directly influences immune function by reducing oxidative damage to cell membranes and their receptors, by influencing the activity of redox-sensitive transcription factors and the production of cytokines and prostaglandins, and by enhancing cell-to-cell communication (Hughes 2001).

These actions are influenced by several factors, such as dose and timing of supplementation, age and health status of the individual. A double-blind, placebo-controlled, randomised crossover study in 25 healthy adult-male non-smokers found that 15 mg/day of beta-carotene enhanced cell-mediated immune responses, with significant increases in the percentages of monocytes expressing the major histocompatibility complex class II molecule HLA-DR and adhesion molecules, as well as increased ex vivo tumour necrosis factor alpha (TNF-alpha) secretion by blood monocytes (Hughes et al 1997). Beta-carotene has also been shown to increase plasma levels of TNF-alpha in patients given 30 mg/day for the treatment of oral leucoplakia (Prabhala et al 1993).

In controlled trials, supplementation with 30 mg beta-carotene was shown to protect against UV-induced photosuppression of immune function in young men (Fuller et al 1992), as well as in older men, with serum beta-carotene levels being significantly associated with maintenance of the delayed-type hypersensitivity response (Herraiz et al 1998). Another controlled trial found that 60 mg/day beta-carotene for 44 weeks increased the CD4–CD8 ratio after 9 months without affecting NK cells, virgin T cells, memory T cells or cytotoxic T cells in healthy male non-smokers; supplementation with 60 mg/day beta-carotene for 4 weeks was shown to significantly increase lymphocyte counts and $CD4^+$ in a pilot study of seven patients with AIDS (Murata et al 1994).

Natural killer-cell activity was also found to increase in older adults in a dose-finding study in which 30 mg/day beta-carotene for 2 months significantly increased in a dose-dependent manner the percentage of lymphoid cells with surface markers for T-helper and NK cells, and cells with IL-2 and transferrin receptors (Watson et al 1991). In a further study of 59 men participating in the Physicians Health Study, 10–12 years of supplementation with 50 mg beta-carotene on alternate days was found to increase NK cell activity without increasing the percentage of NK cells, IL-2 production or receptor expression in elderly but not middle-aged men (Santos et al 1996).

Although beta-carotene supplementation has been shown to enhance NK cell responses, there are a number of randomised controlled trials (RCTs) that suggest that it does not influence other aspects of immune activity in healthy individuals. In separate RCTs, supplementation with 90 mg beta-carotene for 3 weeks or 50 mg on alternate days for more than 10 years was not found to influence T-cell-mediated immunity of healthy elderly people (Santos et al 1997), and supplementation with 30 mg beta-carotene was not found to affect the T-lymphocyte proliferative response to phytohaemagglutinin in healthy lactating and non-lactating women (Gossage et al 2000). Another study found that supplementation with 8.2 mg/day of beta-carotene for 12 weeks did not influence several markers of T-cell-mediated immunity in well-nourished, healthy elderly individuals (Corridan et al 2001).

Antioxidant

Beta-carotene has consistently demonstrated antioxidant activity in vitro, although the mechanism of action is poorly understood. At low partial pressures of oxygen, such as those found in most tissues under physiological conditions, it exhibits good radical-trapping antioxidant behaviour; this capacity is lost at high oxygen pressures in vitro with autocatalytic, pro-oxidant effects observed (Burton & Ingold 1984).

Beta-carotene has been shown to quench singlet oxygen, scavenge peroxyl radicals and inhibit lipid peroxidation in vitro; however, there is ongoing debate about its ability to act as an antioxidant in vivo, with some evidence suggesting this varies from system to system for reasons that are poorly understood (Pryor et al 2000).

Beta-carotene acts synergistically with other antioxidants, such as vitamins E and C, or other dietary components as part of the antioxidant network (see Vitamin E monograph). A combination of beta-carotene and alpha-tocopherol has been shown to inhibit lipid peroxidation significantly more than the sum of the individual inhibitions in a membrane model (Palozza & Krinsky 1992), and a synergistic effect has also been demonstrated in vitro and in vivo with vitamins E and C (Bohm et al 1997, 1998a).

In vivo studies

A number of studies have demonstrated that beta-carotene has antioxidant activity in vivo. Supplementation with 180 mg of beta-carotene for 2 weeks was found to increase the beta-carotene content of LDL and significantly reduce plasma lipid peroxidation and LDL susceptibility to oxidation, as analysed by malondialdehyde generation (Levy et al 1996). Similarly, lipid peroxidation as measured by breath pentane output was found to be significantly reduced in healthy subjects by 4 weeks of daily supplementation with 120 mg of beta-carotene (Gottlieb et al 1993). In a case-controlled trial involving 20 patients with long-standing type 1 diabetes mellitus, as well as age- and sex-matched controls, supplementation with 60 mg/day of natural algae-derived beta-carotene for 3 weeks was found to significantly reduce malondialdehyde and lipid peroxide production and the increased susceptibility towards LDL oxidation seen in the diabetic subjects (Levy et al 2000). Beta-carotene supplementation was also found to significantly reduce serum lipid peroxidation in a dose-dependent manner in a number of double-blind, placebo-controlled trials (Greul et al 2002, Lee et al 2000). Beta-carotene supplementation has also been demonstrated to significantly reduce lipid peroxidation of erythrocytes membranes in people with beta-thalassaemia (Mahjoub et al 2007).

These results contrast with those from a number of studies that failed to demonstrate any in vivo antioxidant activity. A study of 79 healthy volunteers found that normal concentrations of carotenoids in plasma and tissues did not correlate with total antioxidant capacity of the plasma or breath pentane measurements (Borel et al 1998). In other studies

supplementation was seen to increase LDL beta-carotene without changing LDL susceptibility to oxidation (Princen et al 1992, Reaven et al 1993).

It is possible that beta-carotene is more likely to demonstrate antioxidant activity in conditions of increased oxidative stress. This is suggested by the results of a randomised, double-blind controlled trial that involved 42 non-smokers and 28 smokers who received either 20 mg of beta-carotene or a placebo; this trial showed that beta-carotene reduced lipid peroxidation as indicated by breath pentane output in smokers, but not in non-smokers (Allard et al 1994). This is further supported by a study of whole-body irradiation in rats that found that supplementation with natural algae-derived beta-carotene protected against the reduction in growth rate and the selective decline in 9-*cis* beta-carotene and retinol seen in irradiated animals, as well as partially reversing the effect of irradiation when given after the irradiation (Ben-Amotz et al 1996). Algae-derived beta-carotene was also found to protect against CNS oxygen toxicity in rats, as indicated by a significant increase in the latent period preceding oxygen seizures in supplemented animals (Bitterman et al 1994).

Isomer difference

Individual isomers and isomer mixtures demonstrate different antioxidant properties in vivo. The 9-*cis* isomer, which is present in greater amounts in natural beta-carotene, exhibits higher antioxidant potency than the all-*trans* isomer in vitro (Levin & Mokady 1994). Natural beta-carotene, such as that obtained from algal sources, also exhibits greater antioxidant activity than synthetic beta-carotene in vivo (Takenaka et al 1993).

In humans, supplementation with natural algal beta-carotene containing a 50:50 mix of all-*trans* and 9-*cis* isomers has been shown to be a more effective lipophilic antioxidant than all-*trans* beta-carotene (Ben-Amotz & Levy 1996). Human supplementation with natural algal and synthetic beta-carotene has also been shown to produce similar reductions in LDL oxidation, despite the fact that synthetic beta-carotene produced double the rise in LDL beta-carotene content (Levy et al 1995).

These studies contrasted with in vitro studies that suggest that 9-*cis* beta-carotene and all-*trans* beta-carotene have equal antioxidant activities (Liu et al 2000), and that synthetic beta-carotene is twice as effective as algal beta-carotene in inhibiting LDL lipid peroxidation following LDL incubation with copper ions (Lavy et al 1993).

Photoprotection

Beta-carotene, together with other carotenoids, is present in all photosynthetic organisms where it serves an important photoprotective function, either by dissipating excess excitation energy as heat or by scavenging reactive oxygen species and suppressing lipid peroxidation (Penuelas & Munne-Bosch 2005). Studies in bacteria, animals and humans have demonstrated that carotenoids can prevent or lessen photosensitivity by endogenous and exogenous photosensitisers (Mathews-Roth 1993). High doses of beta-carotene (from 180 mg/day up to 300 mg/day) have been used to treat the photosensitivity associated with erythropoietic protoporphyria (Mathews-Roth 1987). There is also consistent evidence from animal and human studies that beta-carotene has photoprotective effects.

Beta-carotene is present at the target sites of light-induced damage in the dermis, epidermis and stratum corneum, with levels varying in skin areas with higher concentration in the forehead and palms (Alaluf et al 2002). Skin levels are related to the levels found in the plasma (Sies & Stahl 2004). Beta-carotene and other endogenous antioxidants are reduced in both skin and blood by UV exposure (Gollnick et al 1996).

Although it is presumed that beta-carotene exerts a light-protective function by quenching excited species such as singlet oxygen and free radicals (Mathews-Roth 1987), there are a number of other ways that beta-carotene may contribute to photoprotection (i.e. protection against the absorption of UV light). These include the protection of target molecules through its antioxidant activity, enhancement of the repair of UV damage, modulation of enzyme activity and gene expression, enhancement of cell-to-cell communication and suppression of cellular responses and inflammation (Sies & Stahl 2004). It is also suggested that the UVA protection provided by beta-carotene is due to the siting of beta-carotene deep inside membranes in proximity to the UVA chromophores that initiate the cell damage (Bohm et al 1998b).

As a strong natural pigment, beta-carotene produces a yellow-orange colouration in the skin that adds to the red colouration from haemoglobin and the brown colouration from melanin to create the normal human skin colour (Alaluf et al 2002). Beta-carotene acts as a blue light filter by absorbing light in the range of 360–550 nanometers (Pathak 1982), with the *cis* isomers having been found to exhibit an additional absorption maximum in the UV range (Sies & Stahl 2004), thus suggesting a possible advantage for natural beta-carotene over synthetic all-*trans* beta-carotene in providing photoprotection.

As with titanium dioxide, the beta-carotene in the skin takes the form of finely dispersed particles that can increase the natural pigment action. This was observed in a human trial involving 20 subjects that found that supplementation with 50 mg of natural algal beta-carotene for 6 weeks increased the reflection capacity of the skin 2.3-fold, irrespective of the wavelength (Heinrich et al 1998). A study on whole albino hairless mouse skin and epidermis, however, suggests that although beta-carotene did impart a visible change in skin colour its absorbance was insufficient to impart significant photoprotection, which indicates that its photoprotective action is mediated through processes in addition to blue light absorption (Sayre & Black 1992).

In a controlled study injection of phytoene, the colourless triene precursor of beta-carotene was found to significantly reduce radiation-induced erythema in guinea pigs (Mathews-Roth & Pathak 1975); however, a further study on albino hairless mice found that 10 g/kg feed of beta-carotene and

200 mg/kg feed of 13-*cis* retinoic acid for 12 weeks did not prevent UVB-induced dermal damage (Kligman & Mathews-Roth 1990).

An in vitro study on human keratinocytes suggests that beta-carotene dose-dependently suppressed UVA-induction of matrix metalloproteases through quenching of singlet oxygen and that this action was not enhanced by vitamin E (Wertz et al 2004). Further studies suggest that beta-carotene also interferes with UVA-induced gene expression by multiple pathways, including inhibition of UVA-induced extracellular matrix degradation, enhanced UVA induction of tanning-associated protease-activated receptor-2, promotion of keratinocyte differentiation and synergistic induction of cell cycle arrest and apoptosis (Wertz et al 2005).

Beta-carotene has also been observed to have synergistic effects with other antioxidants in protecting cultured human fibroblasts from UVA, although only additive effects were observed for UVB (Bohm et al 1998b). The interaction between different antioxidants and/or other as yet unidentified phytochemicals has been used to explain the finding that UV carcinogenesis was enhanced with a beta-carotene-supplemented semi-defined diet in mice (Black 2004, Black & Gerguis 2003, Black et al 2000).

Enhanced intercellular communication

In addition to its antioxidant activity, beta-carotene enhances gap junction intercellular communication by upregulation of the gap junction protein connexin 43. This action may be important in its control of tumour growth (Yeh & Hu 2003) and is likely to be independent of its ability to quench singlet molecular oxygen (Stahl et al 1997).

Animal studies have indicated that a beta-carotene dose of 50 mg/kg/day for 5 days inhibits, whereas a lower dose (5 mg/kg/day) increases gap junction intercellular communication in rat liver. Further in vitro studies suggest that the observed inhibition is due, at least in part, to oxidised beta-carotene (Yeh & Hu 2003).

Anticarcinogenic activity

Observational epidemiological studies have consistently shown a relationship between dietary beta-carotene intake and low risk of various cancers (Cooper et al 1999b, Pryor et al 2000). In animal studies beta-carotene has been found to be chemoprotective, with inhibition of spontaneous mammary tumours (Fujii et al 1993, Nagasawa et al 1991), as well as prevention of skin carcinoma formation (Ponnamperuma et al 2000), UV-induced carcinogenesis in mice (Epstein 1977, Mathews-Roth 1982) and oral cancer in laboratory and animal models (Garewal 1995). Studies in ferrets suggest that the beta-carotene molecule becomes unstable in smoke-exposed lungs and that when given with alpha-tocopherol and ascorbic acid to stabilise the beta-carotene molecule, there is a protective effect against smoke-induced lung squamous metaplasia (Russell 2002).

A review of carotenoid research by the International Agency for Research on Cancer suggests there is sufficient evidence that beta-carotene has cancer-preventive activity in experimental animals, based on models of skin carcinogenesis in mice and buccal pouch carcinogenesis in hamsters (Vainio & Rautalahti 1998), despite a review suggesting that beta-carotene does not protect against lung cancer in animals (De Luca & Ross 1996).

Whether beta-carotene has anticancer properties in humans is unclear. It has been suggested any such effects could be mediated through multiple mechanisms that may include: antioxidant activity preventing oxidative damage to DNA and inhibition of lipid peroxidation; stimulation of gap junction communication; effects on cell transformation and differentiation; inhibition of cell proliferation and oncogene expression; effects on immune function; and inhibition of endogenous formation of carcinogens (Cooper et al 1999a). Additional mechanisms may include the metabolic conversion of beta-carotene to retinoids, which may in turn modulate the gene expression of factors linked to differentiation and cell proliferation. The modulation of enzymes that metabolise xenobiotics and inhibition of endogenous cholesterol synthesis by modulation of HMG-CoA reductase expression may also lead to a possible inhibition of cell proliferation and malignant transformation (PDRHealth 2005).

None of these mechanisms has been conclusively found to contribute to the prevention of cancer in vivo, and there is ongoing debate about the role of beta-carotene in cancer prevention (Cooper et al 1999a, Patrick 2000). This debate has been further fuelled by the findings of two large intervention studies: the Alpha-Tocopherol Beta-Carotene (ATBC) Cancer Prevention Study (the 'Finnish study': Heinonen et al 1994) and the Carotene and Retinol Efficacy Trial (CARET: Omenn et al 1996b), which found a significantly increased risk of lung cancer in high-risk individuals supplemented with synthetic beta-carotene (see *Clinical use* for more details).

The mixed findings from beta-carotene intervention trials have produced much controversy in the scientific literature and although it has been suggested that there is no known biologically plausible explanation for the findings, a number of hypotheses have been put forward (Bendich 2004). It has been suggested that the dose, duration of study and/or choice of synthetic all-*trans*-beta-carotene may have been inappropriate in the intervention trials (Cooper et al 1999b) and that supplementation with monotherapy using synthetic beta-carotene may have inhibited the absorption of other carotenoids (Woodall et al 1996). It is also suggested that, although beta-carotene may be effective in the prevention of lung cancer before or during the phases of initiation and early promotion of cancer, the intervention studies that involved heavy smokers and asbestos workers probably included individuals in whom these processes were already initiated (Bendich 2004).

Additional possible explanations for the observed increase in lung cancer risk with beta-carotene supplementation include possible pro-oxidant activity of beta-carotene or its oxidative metabolites in the high-oxygen environment of smokers' lungs, with oxidised beta-carotene metabolites inducing

carcinogen-bioactivating enzymes, facilitating the binding of metabolites to DNA, enhancing retinoic acid metabolism by P450 enzyme induction and acting as pro-oxidants, causing damage to DNA (Russell 2002) as well as inhibition of retinoid signalling (Wang et al 1999). It is further suggested that the beta-carotene molecule may become unstable due to the presence of a lower level of antioxidants, such as ascorbic acid, in smokers than in non-smokers (Bohm et al 1997), together with the presence of significant oxidative stress in smokers who consume high amounts of alcohol (PDR Health 2005).

It has further been suggested that beta-carotene may increase lung cancer risk in smokers because of its ability to improve lung function. Thus smokers supplemented with beta-carotene may have increased lung capacity, resulting in deeper breathing of carcinogens and other oxidants. It is also suggested that beta-carotene may improve smokers' immune responses and thus reduce the number of days they suffer from upper respiratory tract infections, which enables them to smoke more (Bendich 2004).

The suggestion that beta-carotene may have pro-oxidant effects is supported by an in vitro study showing that although cell viability and DNA integrity were not affected by beta-carotene, they were significantly and dose-dependently decreased by oxidised beta-carotene (Yeh & Hu 2001). There was a dose-dependent increase of beta-carotene cleavage products, together with increasing genotoxicity in vitro when beta-carotene was supplemented during oxidative stress induced by hypoxia/reoxygenation (Alija et al 2004, 2005). Carotenoid cleavage products have also been found to impair mitochondrial function and increase oxidative stress in vitro (Siems et al 2002, 2005), as well as produce a booster effect on phase I carcinogen-bioactivating enzymes in the rat lung (Paolini et al 1999). Beta-carotene has also been shown to be degraded by stimulated polymorphonuclear leukocytes in vitro, producing highly reactive and potentially toxic cleavage products (Sommerburg et al 2003). These pro-oxidant effects have not been conclusively demonstrated in vivo, and beta-carotene at a dose of 50 mg/day for several years was not found to have pro-oxidant effects in either smokers or non-smokers, as measured by urinary excretion of F2-isoprostanes (Mayne et al 2004).

Cardiovascular protection

There are a number of ways in which beta-carotene may act to protect against cardiovascular disease. Free-radical scavenging may prevent cellular transformations leading to atherosclerosis, and protection of LDL oxidation may further act to protect against atheroma formation (Halliwell 1993). Other mechanisms proposed for the possible favourable effect of antioxidants include an increase of HDL cholesterol and the preservation of endothelial functions (Tavani & La Vecchia 1999). Patients with acute myocardial infarction (AMI) have also been shown to have reduced plasma antioxidant vitamins and enhanced lipid peroxidation upon thrombolysis, suggesting that antioxidants may reduce free-radical generation processes in reperfusion injury in AMI (Levy et al 1998).

In an animal study, atherosclerosis was inhibited in rabbits fed a high-cholesterol diet supplemented with all-*trans* beta-carotene. In that study all-*trans* beta-carotene was undetectable in LDL, although tissue levels of retinyl palmitate were increased, suggesting that any anti-atherogenic effect is separate from the resistance of LDL to oxidation and that metabolites of beta-carotene may inhibit atherosclerosis in hypercholesterolaemic rabbits, possibly via stereospecific interactions with retinoic acid receptors in the artery wall (Shaish et al 1995). A randomised, placebo-controlled trial in 149 male smokers taking 20 mg/day of beta-carotene for 14 weeks, however, found no influence on haemostatic measures, suggesting that it is unlikely that cardiovascular protection from beta-carotene is via an effect on haemostasis (Van Poppel et al 1995).

OTHER ACTIONS

An animal study found that rats supplemented with beta-carotene-rich algae had improved reproduction and body growth, with a markedly lower stillbirth rate, a higher litter size or rearing rate, and enhanced body growth in male offspring (Nagasawa et al 1989).

CLINICAL USE

Vitamin A deficiency

In a series of large, double-blind, cluster-randomised, placebo-controlled field trials involving as many as 44,000 Nepalese women, weekly supplementation with 42 mg of *trans*-beta-carotene was found to reduce the prevalence of selected illness symptoms such as loose stools, night blindness and symptoms of high fever during late pregnancy, at the time of birth and during 6 months post-partum (Christian et al 2000b). Beta-carotene was further found to reduce maternal, but not infant, mortality among smokers and non-smokers by approximately 50%, with a protective effect becoming evident after 18 months of supplementation (Christian et al 2004, West et al 1999). Beta-carotene supplementation has also been found to reduce the five-fold increased risk of infection-related mortality in women who were night-blind because of vitamin A deficiency (Christian et al 2000a). In a randomised controlled trial of children in rural China it was found that beta-carotene supplementation had a similar effect on correcting childhood vitamin A deficiency to retinol supplementation, with reduced morbidity and increased weight. The authors concluded that, considering the health risk of vitamin A supplementation and the easier acquisition and antioxidant value of dietary beta-carotene, dietary beta-carotene supplementation should be recommended for addressing vitamin A deficiency in this population (Lin et al 2009).

These studies contrast with one that found an association between self-reports of poor night vision and beta-carotene consumption in women involved in the Blue Mountain Eye Study, in which the authors concluded that perceived poor

night vision caused an increase in carrot consumption in women (Smith et al 1999).

Cancer prevention

There are at least 35 observational epidemiological studies, including prospective cohort and case-controlled studies, involving smoking and non-smoking men and women from diverse regions of the world, which have found a positive association between dietary or serum beta-carotene levels and reduced risk of cancer (Cooper et al 1999a). This association, however, does not necessarily imply a causal link, because it may be an association between beta-carotene ingestion and other dietary or lifestyle factors (Peto et al 1981). Beta-carotene intake is linked to a variety of healthy dietary and lifestyle factors, as well as being highly correlated with the intake of many other protective dietary phytochemicals and nutrients (Cooper et al 1999a). Furthermore, these results have not always been consistent with a 6-year study of 137,001 European men, which found no link between plasma carotenoids and prostate cancer risk (Key et al 2007), and with a pooled analysis of 11 cohort studies suggesting no link with colorectal cancer risk (Männistö et al 2007). Similarly a pooled analysis of 10 cohort studies involving 521,911 women found no association between dietary carotenoids and the risk of ovarian cancer (Koushik et al 2006).

While the protective effect of dietary carotenoids on cancer risk is still being debated, findings of two large intervention trials have reported an increased lung cancer risk with synthetic beta-carotene supplementation (Heinonen et al 1994, Omenn et al 1996a).

The Alpha-Tocopherol Beta-Carotene (ATBC) Cancer Prevention Study, also known as the Finnish study, was the first large intervention trial to test the hypothesis that beta-carotene reduces the risk of lung cancer. This double-blind, placebo-controlled primary-prevention trial involved 29,133 male smokers, 50–69 years of age, who were randomised to receive daily supplementation with alpha-tocopherol (50 mg/day) alone, synthetic (all-*trans*) beta-carotene (20 mg/day) alone, or both. After a follow-up period of 5–8 years, the results suggested that there was an unexpected 18% increase in the incidence of lung cancer with an associated 8% higher mortality among those who received beta-carotene (Heinonen et al 1994). Subgroup analysis revealed that the increased risk with beta-carotene supplementation was only greater for those who smoked at least 20 cigarettes per day, with the risk of those who smoked 5–19 cigarettes/day being no greater than that of the placebo group. An increased risk was also observed for those who consumed more than 11 g/day alcohol compared with those with a lower alcohol intake (Albanes et al 1996). Further analysis found no effect of beta-carotene supplementation on the risk of pancreatic cancer (Rautalahti et al 1999), colorectal cancer (Albanes et al 2000), urothelial or renal cell cancer (Virtamo et al 2000), or gastric cancer (Malila et al 2002).

The Carotene and Retinol Efficacy Trial (CARET) tested the effect of synthetic, all-*trans* beta-carotene (30 mg) and retinyl palmitate (25,000 IU) on the incidence of lung cancer, other cancers and death in 18,314 participants who were at high risk of lung cancer because of a history of heavy smoking or asbestos exposure. CARET was stopped ahead of schedule in January 1996 because participants who were randomly assigned to receive the active intervention were unexpectedly found to have a 28% increase in incidence of lung cancer, a 17% increase in incidence of death and a higher rate of cardiovascular disease mortality compared with participants in the placebo group (Omenn et al 1996b). Further analysis revealed results similar to the ATBC study, with the increased risk of lung cancer being greatest for heavy smokers and those with the highest alcohol intake, while former smokers were found to have a similar risk to that of those taking placebo (Omenn et al 1996b).

The finding of an increased risk of lung cancer in smokers taking beta-carotene in the ATBC and CARET studies is consistent with a number of other studies. A prospective cohort study of 59,910 French women found that self-reported supplemental use of beta-carotene was directly associated with double the risk of cancers among smokers, yet dietary beta-carotene intake was associated with less than half the risk of tobacco-related cancers among non-smokers in a statistically significant dose-dependent relationship (Touvier et al 2005). Similarly, the results of a case-control study of 362 adenoma cases and 427 polyp-free controls suggest a protective effect for colon cancer with beta-carotene in non-smokers and an adverse effect in smokers (Senesse et al 2005). Alcohol intake and cigarette smoking were also observed to modify the effect of beta-carotene supplementation on the risk of colorectal adenoma recurrence in another double-blind, placebo-controlled clinical trial involving 864 patients randomised to receive either beta-carotene (25 mg), vitamin C (1000 mg) or vitamin E (400 mg), beta-carotene with vitamins C and E, or a placebo; after 4 years this trial found no evidence that supplementation reduced the incidence of adenomas (Greenberg et al 1994). Subgroup analysis from this study, however, found that beta-carotene supplementation was associated with a marked decrease in the risk of one or more recurrent adenomas among subjects who neither smoked cigarettes nor drank alcohol, but conferred a modest increase in the risk of recurrence among those who either smoked or drank alcohol and doubled the risk for those who both smoked and drank (Baron et al 2003).

The results of these studies are contrasted with those from the Physicians' Health Study, which found that beta-carotene supplementation had no effect on cancer risk in smokers or non-smokers. This RCT of 50 mg of synthetic beta-carotene given on alternate days involved 22,071 US male physicians, 11% of whom were smokers. After more than 12 years of follow-up, no overall effect on cancer incidence was evident with beta-carotene supplementation (Hennekens et al 1996) and no benefit or harm was observed for lung, prostate or colon cancer (Cook et al 2000), or for squamous cell

carcinoma (Frieling et al 2000). Subgroup analysis of this study population revealed that total cancer was modestly reduced with supplementation among those aged more than 70 years, and total cancers and colon cancer was reduced in those who drank alcohol daily (Cook et al 2000). Total cancers and prostate cancer were also reduced in those in the highest BMI quartile (Cook et al 2000) and those with low baseline beta-carotene levels (Cook et al 1999), while those with high baseline levels had a non-significant increased risk of prostate cancer with beta-carotene supplementation (Cook et al 1999).

Similar to the results of the Physicians' Health Study the results of the Women's Health Study, which involved 39,876 women supplemented with 50 mg of beta-carotene on alternate days for 2 years, found no benefit or harm from beta-carotene supplementation on the incidence of cancer or cardiovascular disease in apparently healthy women, and no benefit or harm observed for the 13% of women who were smokers at baseline (Lee et al 1999).

In contrast to these results, a RCT performed on a poorly nourished population found a lower cancer incidence with beta-carotene supplementation. This study involved 29,584 adults aged between 40 and 69 years from Linxian County, China, which has one of the world's highest rates of oesophageal/gastric cardia cancer and a persistently low intake of several micronutrients. In this study people were randomised to receive retinol and zinc, riboflavin and niacin, vitamin C and molybdenum, or beta-carotene, vitamin E and selenium, at doses that ranged from one- to two-fold the US RDI for a period of 6 years. Results revealed a significantly lower total mortality among those receiving supplementation with beta-carotene, vitamin E and selenium, mainly attributable to lower cancer rates, especially stomach cancer (Blot et al 1993).

Possible reasons for the mixed results

The mixed results from the beta-carotene intervention studies have created significant debate. The results of a review of carotenoid research by the International Agency for Research on Cancer suggest there is a lack of cancer-preventive activity for beta-carotene when it is used as a supplement at high doses (Vainio & Rautalahti 1998). This is supported by a more recent study that examined the relationship between dietary beta-carotene and lung cancer, using pooled data from seven cohort studies that involved 399,765 participants and 3155 lung cancer cases. This study found that dietary beta-carotene intake was not associated with increased or decreased lung cancer risk in those who had never smoked, past or current smokers (Männistö et al 2004). Similarly a recent systematic review and meta-analysis of six randomised clinical trials examining the efficacy of beta-carotene supplements and 25 prospective observational studies assessing the associations between carotenoids and lung cancer suggests that beta-carotene supplementation is not associated with a significant altered risk of developing lung cancer (Gallicchio et al 2008).

The mixed results from beta-carotene intervention studies may also be a reflection of a difference between natural and synthetic beta-carotene, as the negative intervention studies have all used synthetic rather than natural beta-carotene. These studies, however, do provide consistent evidence for a link between dietary and serum beta-carotene levels and reduced cancer risk. Even in the studies that found an adverse effect of beta-carotene supplementation, study participants with the highest intake and serum concentrations of beta-carotene at baseline developed fewer subsequent lung cancers, regardless of their intervention assignment (Albanes 1999, Holick et al 2002). Therefore, although monotherapy with synthetic beta-carotene is no longer generally recommended, there continues to be a consistent call for an increased consumption of beta-carotene-containing foods to assist in the prevention of cancer (Mayne 1996, Pryor et al 2000).

Oral leucoplakia

Beta-carotene consumption has been found to be inversely associated with precancerous lesions of the oral cavity in tobacco users (Gupta et al 1999), and it is suggested that there is a significant role for antioxidant nutrients in preventing oral cancer (Garewal & Schantz 1995). This is supported by the findings of multiple clinical trials in which beta-carotene and vitamin E have been shown to produce regression of oral leucoplakia, a premalignant lesion for oral cancer (Garewal 1994, Wright et al 2007).

In a more recent, double-blind RCT involving 160 people, 360 mg/week of beta-carotene for 12 months was found to induce regression in oral precancerous lesions, with half of the responders relapsing after ceasing supplementation. Similarly, another multicentre, double-blind, placebo-controlled trial found improvement in dysplasia with 60 mg/day of beta-carotene for 6 months (Garewal et al 1999).

These studies are contrasted with a subgroup analysis involving 409 white male cigarette smokers from the ATBC Study, which suggested that beta-carotene supplementation does not play an essential role in preventing oral mucosal changes in smokers (Liede et al 1998).

Cardiovascular disease

Epidemiological studies support the idea that a diet rich in high-carotenoid-containing foods is associated with a reduced risk of heart disease (Kritchevsky 1999). A review of observational and intervention studies on beta-carotene and the risk of coronary heart disease found that seven cohort studies (Gaziano et al 1995a, Gey et al 1993, Knekt et al 1994, Manson et al 1991, Morris et al 1994, Rimm et al 1993, Street et al 1994) reported relative risks between 0.27 and 0.78 for high serum beta-carotene levels or high dietary intake; the review found that this was supported by case-control studies (Bobak et al 1998, Bolton-Smith et al 1992, Kardinaal et al 1993, Torun et al 1994, Tavani et al 1997) that reported odds ratios between 0.37 and 0.71, with a possible stronger protection for current smokers (Tavani & La Vecchia 1999). These results contrast with those of four more recent cohort studies (Knekt et al 1994, Kushi et al 1996, Pandey et al 1995, Todd et al 1995) and five large RCTs

(Hennekens et al 1996, Lee et al 1999, Redlich et al 1999, Vlot et al 1995) that have not reported any significant prevention of cardiovascular disease with beta-carotene supplementation.

The final results of the Physicians' Health Study (see *Cancer prevention* above) indicated that beta-carotene supplementation exerted no significant benefit or harm on cancer or cardiovascular disease during more than 12 years of treatment (Hennekens et al 1996). Similarly, the results of the Women's Health Study, which involved 39,876 women aged 45 years or older, found that beta-carotene supplementation of 50 mg on alternate days did not influence cardiovascular disease after 2 years of supplementation and 2 years of further follow-up. Subgroup analysis revealed that beta-carotene supplementation had an apparent benefit on subsequent vascular events among 333 men with prior angina or revascularisation (Christen et al 2000).

In contrast, analysis of the data from the ATBC cancer prevention study, which involved 23,144 male smokers, found that beta-carotene supplementation slightly increased the risk of angina (Rapola et al 1996) and intracerebral haemorrhage, while having no overall effect on the risk of stroke (Leppala et al 2000a, 2000b), abdominal aortic aneurysm (Tornwall et al 2001), or symptoms and progression of intermittent claudication (Tornwall et al 1999). Beta-carotene, however, was found to decrease the risk of cerebral infarction modestly among a subgroup with greater alcohol consumption (Leppala et al 2000a, 2000b). In a 6-year post-intervention follow-up study, beta-carotene was found to increase the risk of first-ever myocardial infarction, while continuing to have no overall effect on the incidence of stroke (Tornwall et al 2004). An analysis of 52 men from the CARET study concluded that there was no significant effect on total, HDL or LDL cholesterol levels that could account for the increase risk of cardiovascular disease observed in this study (Redlich et al 1999).

A pooled analysis of four randomised trials of beta-carotene therapy ranging from 20 mg to 50 mg involving 90,054 patients found beta-carotene supplementation to be associated with a significant increase in all-cause mortality and cardiovascular death in patients at risk of coronary disease, with the increased risk being strongest in smokers. A further meta-analysis of eight randomised trials involving 138,113 patients found that supplementation with 15–50 mg of beta-carotene was associated with a small but significant increase in all-cause mortality and a slight increase in cardiovascular death (Vivekananthan et al 2003).

The apparent discrepancy between the findings of observational and intervention studies may be due to several factors, including the length and nature of the intervention (Tavani & La Vecchia 1999). For example, the intervention trials involved supplementation with synthetic beta-carotene in isolation or with other single nutrients, whereas the observational studies involved the consumption of beta-carotene-rich foods containing a range of additional antioxidant vitamins, phytonutrients and micronutrients.

Photoprotection

Excessive exposure to solar radiation, especially UVA (320–400 nm) and UVB (290–320 nm), may induce UV-carcinogenesis and erythema in the skin (Lee et al 2000). There have been a number of controlled clinical trials that have demonstrated that supplementation with beta-carotene alone, or in combination with other antioxidants, can reduce UV-induced erythema (Gollnick et al 1996, Heinrich et al 1998, Heinrich et al 2003, Lee et al 2000, Mathews-Roth et al 1972, Sies & Stahl 2004, Stahl et al 2000). These studies suggest that at least 8–10 weeks of supplementation are required before protection against erythema becomes evident and that doses of at least 24 mg/day of beta-carotene are required (Sies & Stahl 2004).

In uncontrolled studies, a protective effect against UV-induced erythema was observed after supplementation with 180 mg of beta-carotene for 10 weeks (Mathews-Roth et al 1972) and with 50 mg for 6 weeks (Heinrich et al 1998). These results are supported by more rigorous studies that have shown photoprotective activity with smaller doses of beta-carotene. An RCT involving supplementation with 30 mg of natural beta-carotene for 8 weeks, with the dose increasing to 60 mg for a further 8 weeks and then to 90 mg for another 8 weeks, found a dose-dependent reduction in UVA- and UVB-induced erythema (Lee et al 2000). In another RCT, supplementation for 12 weeks with 24 mg/day of natural beta-carotene or a natural carotenoid mix supplying similar amounts of beta-carotene, lutein and lycopene also significantly reduced UV-induced erythema (Heinrich et al 2003). Similarly, a randomised trial found that supplementation with 25 mg of natural algal beta-carotene for 12 weeks significantly reduced UV-induced erythema, with the effect enhanced by the addition of alpha-tocopherol (Stahl et al 2000). Yet another trial suggests that the photoprotective action of beta-carotene enhances the action of topical sunscreens. In this randomised, placebo-controlled, double-blind study of 20 healthy young females, 30 mg/day beta-carotene for 10 weeks reduced UV-induced erythema and protected against UV-induced drop in serum beta-carotene levels and UV-induced reduction in Langerhans cells; beta-carotene combined with topical sunscreens was more effective than sunscreen cream alone (Gollnick et al 1996). A protective effect against photo-immunosuppression was demonstrated in another study in which 30 mg/day of beta-carotene for 4 weeks protected against UV-induced suppression of delayed-type hypersensitivity in young men (Fuller et al 1992).

It has been suggested that the duration of supplementation may be more important than the dose, as the studies that have not demonstrated significant reduction in UV-induced erythema have all involved supplementation of relatively short duration (Lee et al 2000). No photoprotective effects were observed with supplementation of 90 mg beta-carotene for 3 weeks (Garmyn et al 1995), 150 mg/day for 4 weeks (Wolf et al 1988) or 15 mg/day for 8 weeks (McArdle et al 2004).

It has also been suggested that a combination of antioxidants may be more effective than the sum of the separate components because the skin's antioxidant defence system appears to involve an intricate connection between individual antioxidants (Steenvoorden & Beijersbergen van Henegouwen 1997). This is supported by a randomised, double-blind, placebo-controlled study that found that short-term (2-week) supplementation with an anti-oxidative combination containing beta-carotene and lycopene, as well as vitamins C and E, selenium and proanthocyanidins, significantly decreases the UV-induced expression of matrix metallo-proteinases, with a non-statistically significant trend towards reduced minimal erythema dose (Greul et al 2002).

Although beta-carotene supplementation may provide some degree of protection against sunburn, the effect is modest and there is still some debate about its use for routine photoprotection (Biesalski & Obermueller-Jevic 2001, Fuchs 1998). However, beta-carotene is likely to be clinically useful in providing photoprotection for people with specific photosensitivity. High doses (180 mg/day, up to 300 mg/day) have been shown to reduce photosensitivity in people with the genetic condition erythropoietic protoporphyria in a number of case series (Mathews-Roth et al 1970, Mathews Roth et al 1974, Thomsen et al 1979), and the results of a double-blind RCT suggest that beta-carotene may be useful in conjunction with canthaxanthin in preventing polymorphous light eruptions (Suhonen & Plosila 1981).

The ability of beta-carotene to protect against UV-induced erythema and photosensitivity does not appear to extend to protecting against non-melanotic skin cancer. In a randomised placebo-controlled trial involving 1805 subjects with recent non-melanotic skin cancer, daily supplementation with 50 mg beta-carotene for 5 years had no effect on the incidence of new or recurring non-melanotic skin cancers, with similar results for those with low-baseline beta-carotene levels and smokers (Greenberg et al 1990). Similarly, in another randomised, placebo-controlled trial of 1621 adults aged between 25 and 74 years, daily supplementation with 30 mg beta-carotene did not reduce the development of solar keratoses over the 3-year study period (Darlington et al 2003, Green et al 1999). These results are supported by an analysis of data from the Physicians' Health Study that found that 12 years of beta-carotene supplementation had no effect on the incidence of non-melanotic skin cancer (Frieling et al 2000); a subgroup analysis from this study also that found no effect on non-melanotic skin cancer in men with low-baseline plasma beta-carotene levels (Schaumberg et al 2004). In a further randomised, placebo-controlled study of 62 patients with numerous atypical naevi, 25 mg of beta-carotene given twice daily for 36 months resulted in a non-significant reduction in newly developed naevi, with a significant reduction observed for the lower arm and feet, but not for ten other body sites (Bayerl et al 2003).

Oxidative stress

There are a number of human studies that suggest that supplementation with beta-carotene can reduce the oxidative stress associated with different pathological conditions or stressors such as intense exercise or radiation. Supplementation with beta-carotene (30 mg/day) and vitamin E (500 mg/day) for 90 days has been found to enhance the antioxidant enzyme activity of superoxide dismutase and catalase in the neutrophils of sportsmen (Tauler et al 2002). Similarly, in a study of 13 professional basketball players, 35 days of antioxidant supplementation with 600 mg alpha-tocopherol, 1000 mg ascorbic acid and 32 mg beta-carotene led to a significant decrease in plasma lipid peroxides, with a significant decrease of lactate dehydrogenase serum activity and a non-significant increase in the anabolic/catabolic balance being observed during a 24-hour recuperation time after exercise (Schroder et al 2001).

The results of an Israeli study of 709 children exposed to radiation from the Chernobyl accident suggest that natural algae-derived beta-carotene may act as an in vivo lipophilic antioxidant or radioprotector. This study found that exposed children had increased susceptibility to lipid oxidation and that supplementation with 40 mg of natural 9-*cis* and all-*trans* equal isomer mixture beta-carotene twice daily for a period of 3 months reduced plasma markers of lipid oxidation (Ben-Amotz et al 1998).

A double-blind study has also found that beta-carotene supplementation reduced the severity, but not the incidence, of post-endoscopy pancreatitis, which is thought to be mediated by oxidative stress (Lavy et al 2004). A further small, controlled trial involving 15 patients with rheumatoid arthritis found that 3 weeks of supplementation with natural beta-carotene resulted in a significant increase in plasma antioxidants, but did not change indicators of disease (Kacsur et al 2002).

There is also evidence that beta-carotene may protect against the oxidative stress caused by chemotherapy and radiotherapy. A study on conditioning therapy found antioxidant protection after supplementation with 45 mg beta-carotene, 825 mg alpha-tocopherol and 450 mg ascorbic acid daily for 3 weeks preceding bone marrow transplantation. The conditioning therapy, which consists of high-dose chemotherapy and total body irradiation, has acute and delayed toxic effects that are considered to be due to peroxidation processes and exhaustion of antioxidants. Supplementation, however, was found to increase serum antioxidant levels and reduce the post-conditioning rise in plasma lipid hydroperoxides in patients receiving the conditioning therapy before transplantation (Clemens et al 1997). A higher then usual dietary intake of beta-carotene has also been found to reduce the occurrence of severe adverse effects of radiation therapy and decrease local cancer recurrence in people with head and neck cancer (Meyer et al 2007).

Contrasting with the above studies are two small studies that showed no change in oxidative stress in healthy subjects after beta-carotene supplementation. Normal concentrations of carotenoids in plasma and tissues were not correlated with clinical

markers of antioxidant and oxidative stress in a study of 79 healthy volunteers (Borel et al 1998), and a placebo-controlled, single-blind study found that daily supplementation with 15 mg of beta-carotene for 3 months did not significantly improve biomarkers of oxidative stress in healthy males (Hininger et al 2001).

Immune function

Beta-carotene supplementation of 15 mg/day has been shown to significantly reduce IgE and respiratory rate and improve recovery of pneumonia among children aged 6–36 months (Mohamed et al 2008). In a study of 652 non-institutionalised elderly people, the incidence of acute respiratory infections was reduced for those with the highest plasma levels, suggesting that beta-carotene may improve the immune response and result in decreased risk of infectious diseases (van der Horst-Graat et al 2004).

In contrast to these findings, analyses of male smokers who participated in the ATBC study found that supplementation with synthetic beta-carotene had no overall effect on the risk of hospital-treated pneumonia or the incidence of the common cold (Hemila et al 2002, 2004), but instead increased the risk of colds in subjects carrying out heavy exercise at leisure but not at work (Hemila et al 2003).

Asthma and chronic obstructive pulmonary disease

Studies have shown increased oxidative stress in patients with chronic airflow limitation (Ochs-Balcom et al 2005) and accumulating evidence suggests that dietary antioxidant vitamins are positively associated with lung function (Schunemann et al 2001), with serum beta-carotene levels being associated with improved forced expiratory volume in the first second (FEV_1) (Grievink et al 2000). Thus it has been suggested that antioxidant protection is important for protecting the lungs against high oxygen levels and that oxidative stress may contribute to respiratory pathology such as asthma (Rahman et al 2006, Wood et al 2003). This is supported by the finding of a significant association between serum vitamin C, vitamin E, beta-cryptoxanthin, lutein/zeaxanthin, beta-carotene, and retinol with FEV_1 (Schunemann et al 2001), together with a study involving a subset from the CARET study of 816 asbestos-exposed men with a high rate of current and former cigarette smoking, which found that serum beta-carotene was associated with a significant improvement in forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) (Chuwers et al 1997).

Studies on the correlation between serum beta-carotene levels and asthma, however, have produced mixed results. A recent meta-analysis of 10 studies on the incidence of dietary antioxidant intake and the risk of asthma found no positive association between intakes of beta-carotene or vitamin E and asthma risk (Gao et al 2008). One small study of 15 asthmatic subjects and 16 healthy controls found that despite similar dietary intake, whole blood levels of total carotenoids — including beta-carotene, lycopene, lutein, beta-cryptoxanthin and alpha-carotene — were significantly lower in the asthmatics, with no differences in plasma or sputum carotenoid levels (Wood et al 2005). Another small study found that beta-carotene, alpha-tocopherol and ascorbic acid were significantly lower in asthmatics at remission compared to controls, and that beta-carotene was significantly lower and lipid peroxidation products significantly higher during attacks than in periods of remission (Kalayci et al 2000). A further small study found that increased dietary consumption of beta-carotene was associated with better quality of life (Moreira et al 2004).

These results are supported by an analysis of 7505 youths (4–16 years) from the Third National Health and Nutrition Examination Survey, which found that increased serum beta-carotene was associated with reduced asthma prevalence (Rubin et al 2004). Another analysis involving 4093 children from the same study, 9.7% of whom reported a diagnosis of asthma, found that asthma diagnosis was associated with lower levels of serum beta-carotene, vitamin C, alpha-carotene and beta-cryptoxanthin (Harik-Khan et al 2004).

In contrast to these findings, a much larger study involving 771 people with self-reported asthma, 352 people with former asthma and 15,418 people without asthma found that asthma status was not significantly associated with serum antioxidant concentrations (Ford et al 2004). Similarly, in a study of 15 mild asthmatics and 15 age- and sex-matched controls, oxidative stress was found to be increased in the asthmatics, with no difference in plasma dietary antioxidant vitamins (Wood et al 2000).

Although the role of antioxidant vitamins in prevention and/or treatment of asthma remains to be determined (Kalayci et al 2000), the results of one intervention study suggest that there may be a role for beta-carotene in exercise-induced asthma. This randomised, double-blind, placebo-controlled trial involved 38 subjects with proven exercise-induced asthma and found that supplementation with 64 mg/day of natural algal beta-carotene for 1 week protected against post-exercise reduction in FEV_1 (Neuman et al 1999).

Cystic fibrosis

Cystic fibrosis (CF) is characterised by exocrine pancreatic insufficiency and reduced absorption of fat-soluble vitamins, as well as by chronic lung inflammation and an associated increased oxygen free-radical generation. Patients with CF have been found to have lower levels of beta-carotene, and it has been suggested that they would benefit from beta-carotene supplementation (Cobanoglu et al 2002, Walkowiak et al 2004). This suggestion is supported by a study of 52 patients with CF, which found a statistically significant correlation between serum beta-carotene and the clinical course of the disease as indicated by faecal elastase-1 and FEV_1 (Walkowiak et al 2004), together with a study showing that the plasma levels of beta-carotene and vitamin E increased and the plasma levels of TNF-alpha and malondialdehyde decreased after 6 months of beta-carotene supplementation (Cobanoglu et al

2002). This is further supported by a RCT of 24 CF patients who were supplemented with up to 50 mg/day beta-carotene for 12 weeks and 10 mg/day beta-carotene for a further 12 weeks; a significant decrease in oxidative stress, correction of total antioxidative capacity and improved pulmonary response to treatment were found in the supplemented group (Rust et al 2000).

Cataracts

Although a high intake of foods containing beta-carotene has been associated with the prevention of cataracts, the role of supplementation is uncertain. An assessment of dietary beta-carotene intake in a subgroup of 472 non-diabetic female participants aged 53–73 years in the Nurses' Health Study found that the odds of posterior subcapsular cataracts were 72% lower in those with the highest intakes of beta-carotene who had never smoked, whereas beta-carotene intake and cataract risk were not associated in current or past smokers (Taylor et al 2002). In contrast to this finding, intervention studies have shown that beta-carotene may help prevent cataracts in smokers (Christen et al 2003, 2004). Two years of beta-carotene treatment was found to have no significant beneficial or harmful effect on the development of cataract in a randomised, double-masked, placebo-controlled trial of 39,876 female health professionals aged 45 years or older who participated in the Women's Health Study, although a subgroup analysis suggests a possible beneficial effect in smokers (Christen et al 2004). Similarly, the Physicians' Study (see above) found that 12 years of supplementation did not reduce the overall incidence of cataracts or cataract extraction; however, in a subgroup of smokers the risk of cataract was reduced by approximately 25% (Christen et al 2003).

In two randomised, double-masked trials that involved 5390 nutritionally deprived subjects in Linxian, China, supplementation with selenium, alpha-tocopherol and beta-carotene for 5–6 years was found to significantly reduce the prevalence of nuclear, but not cortical, cataracts in older subjects (Sperduto et al 1993). This contrasts with the finding that 500 mg of vitamin C, 400 IU of vitamin E and 15 mg of beta-carotene had no apparent effect on the 7-year risk of development or progression of age-related lens opacities or visual acuity loss in a relatively well-nourished older adult cohort of 4629 people, aged from 55 to 80 years, who participated in the Age-Related Eye Disease (ARED) study (Kassoff et al 2001).

Age-related macula degeneration

Although beta-carotene and other nutrients may have been found to be beneficial for preventing age-related macula degeneration (ARMD), the carotenoids lutein and zeaxanthin appear to provide the most protection (see monograph *Lutein and zeaxanthin*).

A high intake of beta-carotene-containing foods has been associated with the prevention of ARMD, and observational and experimental data suggest that carotenoid supplements may delay progression of both ARMD and vision loss. This is supported by the findings from the ARED study, in which an 11-centre, double-masked clinical trial involving 3640 participants with ARMD found that supplementation with vitamin C 500 mg, vitamin E 400 IU, beta-carotene 15 mg and zinc 80 mg for 6 years significantly reduced the development of advanced ARMD and moderate visual acuity loss (Kassoff et al 2001). This result contrasts with findings from the Physicians' Study (see above), which found no beneficial or harmful effects of beta-carotene supplementation on the incidence of ARMD (Christen et al 2007).

Erythropoietic protoporphyria and photosensitivity

Studies in bacteria, animals and humans have demonstrated that carotenoid pigments can prevent or lessen photosensitivity to endogenous photosensitisers, such as chlorophyll or porphyrins, as well as to exogenous photosensitisers (Mathews-Roth 1993). High doses of beta-carotene (between 180 and 300 mg/day) have been used to effectively prevent or lessen photosensitivity in most patients with erythropoietic protoporphyria and in some patients with other photosensitivity diseases such as solar urticaria, hydroa aestivale, porphyria cutanea tarda and actinic reticuloid (Mathews-Roth 1986, 1987, Mathews-Roth et al 1977).

Cognitive function

A study of cognitive function in high-functioning older people found that beta-carotene may offer protection from cognitive decline in people with a greater genetic susceptibility, as evidenced by the presence of the apolipoprotein E4 allele (Hu et al 2006). There is also evidence to suggest that long-term supplementation with beta-carotene may provide cognitive benefits, whereas short-term supplementation does not. A study examining cognitive function in 5956 participants older than 65 years in the Physicians' Health Study found significant higher cognitive function in the beta-carotene group when 4052 continuing participants who had been receiving either beta-carotene supplementation or a placebo for an average of 18 years were examined, but no difference was found between the beta-carotene and placebo groups in 1904 newly recruited subjects after 1 year of intervention (Grodstein et al 2007).

DOSAGE RANGE

Consumption of the recommended five or more servings of fruits and vegetables per day provides 3–6 mg of beta-carotene. Supplemental intake of beta-carotene ranges from 3 to 30 mg/day, although medicinal doses to treat erythropoietic protoporphyria or prevent a reaction to sun in patients with polymorphous light eruption range from 30 to 300 mg/day (PDRHealth 2005). The dose required to provide photoprotection is greater than 24 mg/day for more than 2 months (Sies & Stahl 2004).

To enhance absorption, supplementation should be taken with meals.

TOXICITY

Beta-carotene is readily converted into vitamin A when required by the body and is considered to be non-toxic, even when given in doses as high as 300 mg/day (Mathews-Roth 1990b, 1993).

A review of the literature on adverse effects of carotenoids on human and animal development suggests that beta-carotene does not have any genotoxic affects (Mathews-Roth 1988), and a toxicity study performed on rats suggests a no-observed-adverse-effect-level (NOAEL) is at a dietary level of at least 5%, or more than 3000 mg/kg/day (Nabae et al 2005). Beta-carotene overdose is not reported in the literature.

ADVERSE REACTIONS

At doses greater than 30 mg/day, beta-carotene may cause an orange-yellow colouration of the skin (carotenodermia), which is usually seen first as yellowness of the palms and soles. This condition is harmless and reversible when intake ceases (Micozzi et al 1988). Carotenodermia is distinguished from jaundice by the absence of yellowed ocular sclerae. For some people, this skin colouration is actually considered desirable (Mathews-Roth 1990a) and is utilised in tanning tablets to produce a natural-looking skin tan (DerMarderosian & Beutler 2002).

At present it is unclear if there is a true link between increased lung cancer risk and long-term beta-carotene supplementation in smokers, because supplementation studies with synthetic beta-carotene have produced mixed results: two studies demonstrated an increased lung cancer risk in heavy smokers or those with high asbestos exposure (Group 1994, Heinonen et al 1994, Omenn et al 1996a), while other studies found either no effect (Hennekens et al 1996, Lee et al 1999) or a protective effect (Blot et al 1993).

The association between increased lung cancer risk and beta-carotene has not been found with natural beta-carotene, and there is no suggestion that heavy smokers should reduce their intake of beta-carotene-rich foods. A review suggests that there is no evidence at present that consuming small amounts of supplemental beta-carotene in a multivitamin tablet at amounts that exist in foods (< 6 mg) is unwise for any population (Pryor et al 2000).

SIGNIFICANT INTERACTIONS

Drugs reducing fat absorption

Drugs that reduce fat absorption, such as cholestyramine, colestipol and orlistat, may also reduce absorption of beta-carotene (PDRHealth 2005). This can be avoided by spacing the administration of these substances by at least 2 hours. Plant sterols have been found to reduce beta-carotene bioavailability by approximately 50% in normocholesterolaemic men (Richelle et al 2004).

Fibrates

There may be a positive interaction between fibrate and natural beta-carotene, which has been found to significantly increase HDL cholesterol levels in fibrate-treated mice and humans (Shaish et al 2006).

Valproate

Epileptic patients who gain weight with valproate therapy have been found to have reduced plasma concentrations of beta-carotene and other fat-soluble antioxidant vitamins; this is reversible after valproate withdrawal (Verrotti et al 2004).

CONTRAINDICATIONS AND PRECAUTIONS

Heavy smokers should be advised not to take synthetic beta-carotene supplements for long periods of time.

PREGNANCY USE

Beta-carotene crosses the placenta. Adequate and well-controlled studies in humans have not been documented. No problems with pregnancy have been documented in women taking up to 30 mg beta-carotene daily (Micromedex 2003). As vitamin A is vital for the development of the fetus and the newborn baby, it has been recommended that pregnant women increase their vitamin A intake by 40% and breastfeeding women by 90%. It is further suggested that increasing dietary beta-carotene is an effective way for women to maintain their vitamin A levels (Strobel et al 2007).

PRACTICE POINTS/PATIENT COUNSELLING

- Beta-carotene is an antioxidant found in carrots, other vegetables and fruits, as well as in seaweed and algae. Together with other carotenoids, it is an effective marker for a diet rich in fruits and vegetables.
- Beta-carotene is fat soluble and should be consumed with meals.
- Although beta-carotene is converted into vitamin A in the body, unlike vitamin A it is considered non-toxic even in large doses.
- When supplementing with beta-carotene, it is preferable to use supplements containing natural beta-carotene from the algae *Dunaliella salina* or palm oil, rather than synthetic beta-carotene.
- Beta-carotene is a powerful pigment that contributes to the normal yellow component of skin, and increased beta-carotene intake may protect from the effects of excessive exposure to sunlight and the symptoms of sunburn.
- Consumption of beta-carotene-rich food is associated with reduced risk of cancers, heart disease and eye disease; however, these benefits have not been found in large studies that have used synthetic beta-carotene, with two studies finding an increase in lung cancer in heavy smokers and asbestos workers taking large doses of synthetic beta-carotene.

PATIENTS' FAQs

What will this supplement do for me?

Beta-carotene supplementation will ensure you maintain adequate vitamin A levels. It may possibly assist in preventing cancer and cardiovascular disease, help maintain a healthy immune system, prevent sunburn and photoageing of the skin, assist with asthma, and deal with oxidative stress.

When will it start to work?

It may take up to 2–3 months to see a benefit with UV protection, whereas other benefits may be observable only over many years.

Are there any safety issues?

Beta-carotene is considered non-toxic. Large doses may cause a yellowing of the skin, but this is harmless and reversible.

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Bilberry

HISTORICAL NOTE Bilberries have been used as a food for many centuries and are valued for their taste and high nutritional content. They are still commonly used to make jams, pies, syrups and beverages. Medicinally, the berries have been used internally to treat diarrhoea and haemorrhoids and externally for inflammation of the mouth and mucous membranes as they have significant astringent activity. According to folklore, World War II British Royal Air Force pilots noticed that their night vision seemed to improve after consuming bilberries or bilberry preserves, sparking a renewed interest in the medicinal properties of the fruits.

COMMON NAME
Bilberry

OTHER NAMES
Baies de myrtille, blaubeeren, dwarf bilberry, European bilberry, European blueberries, huckleberry, hurtleberry, heidelbeeren, petit myrte, whortleberry, wine berry

BOTANICAL NAME/FAMILY
Vaccinium myrtillus (family Ericaceae)

PLANT PARTS USED
Dried ripe fruit or fresh fruit (berries)

CHEMICAL COMPONENTS
The fruit contains catechin tannins (up to 10%), invert sugar, fruit acids, flavonol glycosides including astragalin, hyperoside, isoquercitrin and quercitrin, phenolic acids, pectins, triterpenes, and polyphenols such as anthocyanosides. The volatile oil includes methyl salicylate, farnesol, vanillin, myristicin and citronellol. Bilberry also contains vitamin C and chromium, which are suspected of playing a role in its pharmacological activities.

Some of the anthocyanosides are responsible for the deep blue pigment of the fruit (Kahkonen et al 2001). As the fruit ripens, the anthocyanoside content increases. Some commercially available extracts are standardised to anthocyanoside content. Recent research indicates that the anthocyanidin content is particularly high in the pulp of the fruit, however, all parts of the fruit are potential sources of phenolic compounds (Riihinen et al 2008). Anthocyanin concentration in the fresh fruit is approximately 0.1–0.5%, while concentrated bilberry extracts are usually standardised to 25% anthocyanins (Ichiyanagi et al 2004, Zhang et al 2004).

Clinical note — Tannins
Tannins are polyphenolic compounds that have an affinity for proteins. They also complex with alkaloids and therefore should not be mixed with alkaloid-containing herbs.

Anthocyanosides are condensed tannins. When they come into contact with mucous membranes they have an astringent action, making the mucosa less permeable. This activity has been used therapeutically in a variety of ways.

Taken internally, herbs with a high tannin content such as bilberry have been used to treat diarrhoea; applied externally, a styptic action occurs that reduces blood loss.

MAIN ACTIONS
The pharmacological actions of bilberry have not been significantly investigated in clinical studies, so information is generally derived from in vitro and animal studies or based on known information about key constituents found within the herb. Most of the research undertaken to understand the pharmacology of the herb has focused on the anthocyanoside content.

Antioxidant
Anthocyanosides are the main phenolic constituents in bilberry and have well established antioxidant activity (Kahkonen et al 2001, Roy et al 2002). This activity is believed to be primarily due to their chemical structure (Mozaffarieh et al 2008, Yao et al 2007). Anthocyanosides have exhibited superoxide radical scavenging properties and cytoprotective activity against oxidative damage in animal models (Valentova et al 2007).

Reduces ischaemic reperfusion injury
Bilberry anthocyanosides have been shown to improve ischaemic damage, preserve capillary perfusion, inhibit increased permeability of reperfusion and save arteriolar tone in an animal model of ischaemic reperfusion injury (Bertuglia et al 1995).

Ophthalmic conditions
Bilberry's significant antioxidant activity is believed to be responsible for much of its activity in the eye, in particular, prevention of cataract.

Anti-inflammatory and anti-oedema activity
Biochemical and histochemical data show that the anthocyanins decrease vascular permeability and alter capillary wall dynamics by increasing the

Clinical note — Cataract
Growing evidence suggests that senile cataract development may in part be linked to the endogenous generation of free radical molecules, such as superoxide derived from oxygen and light in the aqueous humour and lens (Varma & Richards 1988, Varma et al 1982, 1994). As such, substances with significant antioxidant activity such as anthocyanins, vitamin C and vitamin E have been investigated as potential prophylactic treatments.

endothelium barrier effect via stabilising membrane phospholipids and increasing synthesis of the mucopolysaccharides in the connective ground substance, thus restoring the altered pericapillary sheath (Mian et al 1977).

These effects have been demonstrated in animal models for both oral administration and topical application of bilberry anthocyanins (1% alcohol solution) and were seen to be stronger and longer lasting than those of rutin (Lietti et al 1976).

Astringent

The astringent properties of bilberry are well established and attributed to its significant tannin content.

Improves visual function

Epidemiological investigations have indicated that moderate consumption of anthocyanin-containing herbs such as bilberry extract is associated with an improvement of visual function (Hou 2003). Several animal studies suggest a positive effect on dark adaptation (Canter & Ernst 2004). More specifically, bilberry enhances regeneration of rhodopsin in the retina, which is essential for optimal functioning of the rods and therefore light adaptation and night vision (Blumenthal et al 2000). Other possible mechanisms of action in the eye include accelerated modulation of retinal enzyme activity and improved microcirculation (Canter & Ernst 2004).

Jang et al 2005 demonstrated that two anthocyanins from bilberry were potent antioxidants that suppressed photo-oxidative processes initiated in retinal pigment epithelial (RPE) cells by A2E, which is associated with ageing and some inherited forms of retinal degeneration (Kim et al 2008).

Gastroprotective activity

In vitro results have found that a specific anthocyanin found in bilberry causes an increase in the efficiency of the gastric mucosal barrier (Cristoni et al 1989). When administered orally in an animal model it retarded the development of gastric ulcers induced by stress, NSAIDs, ethanol, reserpine and histamine (Magistretti et al 1988).

Hypoglycaemic activity

A dried hydroalcoholic extract of bilberry leaf administered orally to streptozotocin-diabetic rats for 4 days decreased plasma glucose levels by 26% (Cignarella et al 1996).

Reduces triglyceride levels

A dried hydroalcoholic extract of bilberry leaf administered orally to streptozotocin-diabetic rats for 4 days decreased plasma triglyceride levels by 39% (Cignarelli et al 1996).

Neuroprotective

Anthocyanoside content is beneficial in reversing the course of neurodegeneration in animals by affecting calcium homoeostasis and improving motor performance (Kolosova et al 2006, Landfield et al 1994).

Anticarcinogenic activity

Preliminary research has found that components of the hexane/chloroform fraction of bilberry exhibit anticarcinogenic activity (Bomser et al 1996). More recently, antiangiogenic activity has also been identified (Roy et al 2002) as well as anticarcinogenic activity via inhibition of the nuclear factor-kappa B activation pathway (Aggarwal et al 2006). One animal study demonstrated significant reduction in colon cancer in animals fed an anthocyanidin mixture derived from bilberry (Cooke et al 2006).

OTHER ACTIONS

Bilberry extract inhibits platelet aggregation according to ex vivo tests (Pulliero et al 1989).

CLINICAL USE

Bilberry extracts are popular in Europe and have been investigated in numerous clinical trials, primarily in non-English speaking European countries. As a result, many research papers have been published in other languages. To provide a more complete description of the evidence available, secondary sources have been used when necessary.

Non-specific acute diarrhoea

The considerable astringent activity of bilberry provides a theoretical basis for its use in non-specific acute diarrhoea. Commission E approved crude fruit preparations for this indication (Blumenthal et al 2000).

Mild inflammation of the mouth and throat

The considerable astringent, anti-inflammatory and anti-oedema activity of bilberry provides a theoretical basis for its use as a topical application in these indications. Commission E approved this indication (Blumenthal et al 2000).

Haemorrhoids, varicose veins, venous insufficiency

The considerable astringent, anti-inflammatory and anti-oedema activity of bilberry provides a theoretical basis for its use in these conditions. Several human case series and a single-blind trial report significant improvements in lower extremity discomfort and oedema related to chronic venous insufficiency; however, further research is required to confirm these findings (Ulbricht & Basch 2005).

Pregnancy

A bilberry product (Myrtocyan®) was taken at a dose of 320 mg daily in the last trimester by women aged 24–37 years with pregnancy-induced lower extremity oedema and found to significantly improve symptoms of burning and itching, heaviness, pain, diurnal and nocturnal leg cramps, oedema and capillary fragility (Ghiringhelli et al 1978 and reported in Blumenthal 2003).

Ophthalmic conditions

Bilberry preparations have been used to improve poor night vision, light adaptation and photophobia, myopia and to prevent or retard diabetic retinopathy, macular degeneration and cataracts.

Primarily the collagen-enhancing and antioxidant activities of bilberry provide a theoretical basis for these indications.

Visual acuity and light adaptation

A systematic review of 12 placebo-controlled trials (5 RCTs and 7 placebo-controlled non-randomised trials) concluded that the anthocyanosides from *Vaccinium myrtillus* were not effective for improving night vision; however, the authors point out that the potential therapeutic role of these constituents should not yet be dismissed because confounding factors and supportive auxiliary evidence exists (Canter & Ernst 2004). Four of the RCTs showed no positive effects for *V. myrtillus* anthocyanosides on outcome measures relevant to vision in reduced light whereas the fifth RCT and all seven non-randomised trials reported positive effects on outcome measures relevant to night vision. Seventeen other studies were located by Canter and Ernst but not included in the analysis because they did not contain a placebo group. Sixteen of those studies produced positive results on measures relevant to night vision in either healthy subjects or patients with a range of visual disorders and only one was negative.

The authors point out several confounding factors, in particular the wide range of doses, possible geographical variations in extract composition, choice of subject (generally healthy) and methods used to obtain and interpret electroretinograms, which varied between older and newer studies. For example, two of the negative RCTs tested the lowest dose levels of any of the trials: 36 mg daily for acute treatment and ≤ 48 mg for short-term treatment.

A significant improvement in visual performance has been demonstrated for bilberry extract in people with retinitis pigmentosa and haemeralopia (inability to see distinctly in bright light), suggesting that effects may be more pronounced in cases of impaired visual acuity (Gloria & Peria 1966, Junemann 1967).

Glaucoma

In one small study of eight patients, a single oral dose of 200 mg bilberry anthocyanosides was shown to improve glaucoma, as assessed by electroretinography (Caselli 1985).

Retinopathy

In Europe, bilberry anthocyanoside extracts are recognised as highly effective in preventing or treating diabetic retinopathy, with clinical research supporting its use (Lietti et al 1976, Orsucci et al 1983, Perossini et al 1987, Scharrer & Ober 1981).

One double-blind study involving 40 patients with diabetic and/or hypertensive retinopathy showed that a dose of bilberry extract (Tegens™) equivalent to 160 mg anthocyanosides taken twice daily for 1 month significantly improved ophthalmoscopic parameters and angiographic parameters (Perossini et al 1987). Another study of 31 subjects with different forms of retinopathy (diabetic retinopathy, retinitis pigmentosa, macular degeneration or haemorrhage due to anticoagulant use) found that treatment with bilberry extract (Difrarel 100™) reduced vascular permeability and the tendency to haemorrhage in all patients (Scharrer & Ober 1981). A small open study by Orsucci et al of 10 subjects with diabetic retinopathy found that 6 months of treatment with bilberry extract (Tegens™) equivalent to 240 mg anthocyanosides daily resulted in reduction or disappearance of haemorrhages and improvement in the retinal picture (Orsucci et al 1983 and reported in Blumenthal 2003).

Myopia

Uncontrolled trials report a beneficial effect of the extract on patients with myopia (Canter & Ernst 2004).

Additional studies using purified anthocyanoside oligomers highlight significant improvements in subjective symptoms and objective contrast sensitivity in myopia patients with poor night vision (Lee et al 2005). However, as specificity of source is not provided, this information can only be used in conjunction with the additional supportive evidence listed above.

Cataract

In practice, bilberry has been recommended to delay cataract progression. A case series of 50 elderly subjects with early-stage cataract found that a combination of anthocyanosides extracted from bilberry and vitamin E slowed progression of lens opacities by 97% (Ulbricht & Basch 2005). Placebo-controlled trials are now required to confirm these results.

OTHER USES

Traditionally, bilberry has been used to treat dysentery, diabetes, gastrointestinal inflammatory conditions, vaginal discharges, haemorrhoids, and to stop lactation. Externally, bilberry preparations have been used to treat wounds, ulcers and skin infections. More recently, other uses include treatment for bleeding gums, nose bleeds, spider veins, capillary fragility, peptic ulcers, Raynaud's syndrome and venous insufficiency (such as claudication).

Additionally, a double-blind placebo-controlled study confirmed that bilberry improves peripheral vascular disorders by improving subjective symptoms after 30 days' treatment (Mills & Bone 2000).

DOSAGE RANGE

Internal

- Fluid extract (1:1) standardised to provide 60–120 mg daily of anthocyanins: 6–12 mL/day taken in three divided doses.
- Oral dose forms: bilberry extracts providing 240–480 mg of anthocyanins daily.
- Decoction of dried herb: 5–10 g of crushed, dried fruit in 150 mL of cold water, which is then boiled for up to 10 minutes and strained while hot. For symptomatic treatment of diarrhoea, drink the cold decoction several times daily.
- Gargle: a 10% decoction of the above preparation.
- Fresh berries: 165–345 g daily.

External
- 5–10 g crushed dried fruit in 150 mL of cold water, brought to the boil for 10 minutes then strained while hot to make a decoction for local application.

TOXICITY
Rats administered high doses of up to 400 mg/kg showed no adverse effects (Murray 1995).

ADVERSE REACTIONS
No adverse effects were reported in a systematic review of 12 placebo-controlled trials of *V. myrtillus* anthocyanosides (Canter & Ernst 2004). According to the same authors, a post-marketing surveillance study of 2295 people identified that 4% experienced side-effects related to the skin, nervous system or gastrointestinal tract.

SIGNIFICANT INTERACTIONS
Controlled studies are not available, therefore interactions are theoretical and based on evidence of pharmacological activity with uncertain clinical significance.

Anticoagulant and antiplatelet drugs
A theoretical risk exists that high doses (>170 mg anthocyanidins) may increase bleeding risk, however, this remains uncertain as there is inadequate clinical evidence (Stargrove et al 2008).

Iron
Reduced absorption is theoretically possible if taken at the same time because of the tannin content of the herb — separate doses by 2 hours.

Hypoglycaemic agents
Additive effects are theoretically possible with leaf preparations — observe patient.

CONTRAINDICATIONS AND PRECAUTIONS
High doses (>170 mg anthocyanidins) should be used with caution by people with haemorrhagic disorders.

PREGNANCY USE
A study investigating bilberry extract for pregnancy-induced lower extremity oedema reported no adverse effects (Ulbricht & Basch 2005) — likely to be safe when berry is consumed in dietary amounts.

PATIENTS' FAQs
What will this herb do for me?
Bilberry is used to relieve the symptoms of mild diarrhoea and improve poor night vision, sensitivity to glare, photophobia, peptic ulcers, varicose veins, venous insufficiency and haemorrhoids when taken internally. It is also used as a mouthwash, gargle or paint for mild inflammation of the mouth or throat, such as gingivitis or pharyngitis.

When will it start to work?
This depends on the indication. Improvements in night vision, photophobia and glare sensitivity have been reported within 2–4 weeks of use in some people whereas preventive effects are likely to require long-term use. In peripheral vascular diseases, 30 days' treatment may be required before effects are noticed.

Are there any safety issues?
Considered a safe herb overall, bilberry can theoretically reduce blood glucose levels in people with diabetes and so should be used carefully in these patients. At very high doses it may interact with warfarin and antiplatelet drugs.

PRACTICE POINTS/PATIENT COUNSELLING
- Bilberry has antioxidant, anti-inflammatory and astringent actions and has considerable polyphenol content.
- Bilberry extract is a popular treatment in Europe for preventing and treating retinopathy. It is also used to treat several other ophthalmic conditions such as poor night vision, poor light adaptation, and sensitivity to glare, photophobia, glaucoma, myopia and cataract.
- Some research also suggests that it is useful in venous insufficiency, peripheral vascular disorders (such as Raynaud's syndrome) and capillary fragility.
- Approved by Commission E for the treatment of non-specific, acute diarrhoea and mild inflammatory conditions of the mouth and throat.
- Preliminary evidence suggests it may reduce serum glucose levels and triglycerides in diabetes and prevent peptic ulcer formation due to NSAIDs or stress; however, clinical research is still required to confirm these effects.
- In vitro investigation has identified anticarcinogenic activity.

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Bitter melon

HISTORICAL NOTE Bitter melon is used as a traditional medicine wherever it is found. It has a long history of use in Asia, Africa and Latin America and has been widely acclaimed as an important remedy for diabetes mellitus since ancient times. The term *momordica* means 'to bite' and refers to the jagged edges of the leaf, which appear as if bitten. Bitter melon has been used to treat fevers, viral infections and as an emmenagogue in reproductive health. It has also been used to treat gastrointestinal complaints, worms, constipation, headaches, skin conditions and diabetes. The fruit is used topically for wound healing. The plant has also been used in traditional ceremonies and considered a powerful charm, which is worn as a necklace, wrist or ankle bracelet or crown (Beloin et al 2005). The ritual ceremonial importance of the plant is accompanied by its considerable reputation as a medicinal plant for the treatment of disease.

OTHER NAMES

African cucumber, balsam pear, bitter gourd, kakara, karela, ku gua, sushavi, wild cucumber

BOTANICAL NAME/FAMILY

Momordica charantia (family Curcubitaceae)

PLANT PARTS USED

Fruit, leaves

CHEMICAL COMPONENTS

It contains several biologically active constituents that include glycosides (e.g. momordicins I and II), steroidal saponins (e.g. charantins), alkaloids, fixed oils and proteins (e.g. MAP 30: Momordica anti-HIV protein; molecular weight, 30 kD). The immature fruits are a good source of vitamin C and also provide vitamin A, phosphorus, and iron (Grover & Yadav 2004).

MAIN ACTIONS

Bitter melon has been the subject of countless studies and has demonstrated significant pharmacological activity in a variety of experimental models.

Antidiabetic

The antidiabetic potential of bitter melon is well established in normal, streptozocin- or alloxan-induced diabetic animals and in genetic models of diabetes (Ahmed et al 2004, Bailey et al 1985, Chaturvedi 2005, Day et al 1990, Harinantenaina et al 2006, Jayasooriya et al 2000, Kar et al 2003, Miura et al 2001, 2004, Ojewole et al 2006, Reyes et al 2006, Sarkar et al 1996, Shetty et al 2005, Shibib et al 1993). All parts of the plant (fruit pulp, seeds, leaves and whole plant) have shown activity.

A systematic study comparing the hypoglycaemic activity of three extracts in vivo found that the methanolic extract of dried whole fruits and seeds reduced blood glucose by 49% at the end of the first week, which became 39% by week 5; the aqueous extract of fresh, unripe, whole fruits reduced fasting blood glucose by 50%, which was consistent until the study ended, and the chloroform extract of dried whole fruits and seeds showed almost no hypoglycaemic activity (Virdi et al 2003).

These observations have special significance when one considers that the whole bitter gourd is cooked in water and consumed in many cultures, particularly in India.

The hypoglycaemic activity is attributed to a mixture of steroidal saponins known as charantins, insulin-like peptides and alkaloids that are concentrated in the fruit (Grover & Yadav 2004), whereas several different fractions of *Momordica charantia* extract may make different contributions to its cell repairing activity and its ability to stimulate insulin secretion (Xiang et al 2007).

At least eight clinical studies of different designs have investigated the hypoglycaemic activity of bitter gourd preparations producing mostly positive results. Of note, most studies are small and statistical analyses are poorly described. Large-scale clinical trials are required before clinical significance can be confirmed.

Based on studies with animal models, it appears that *Momordica charantia* increases the renewal of beta-cells in the pancreas, or may permit the recovery of partially destroyed beta-cells (Ahmed et al 1998, Fernandes et al 2007, Singh & Gupta 2007, Xiang et al 2007), and stimulates pancreatic insulin secretion (Fernandes et al 2007, Welihinda et al 1982). It also improves peripheral glucose uptake (Fernandes et al 2007, Welihinda & Karunanayake 1986), improves insulin sensitivity and insulin signaling (Sridhar et al 2008). A study with streptozocin-induced diabetic animals found that bitter melon juice normalises the structural abnormalities of peripheral nerves, regulates glucose uptake into the jejunum membrane brush border vesicles and stimulates glucose uptake into skeletal muscle cells (Ahmed et al 2004). A recent study of streptozocin-induced diabetic animals further reveals a beneficial role for bitter gourd in controlling glycoconjugate- and heparan sulfate-related kidney complications in diabetes thus prolonging late complications of diabetes (Kumar et al 2008).

Lipid-lowering

Lipid-lowering activity has been reported in studies of normal and diabetic animals for the fruit extract, flavonoids extracted from bitter melon or a methanolic fraction of the plant (Ahmed et al 2001, Anila & Vijayalakshmi 2000, Chaturvedi 2005, Chaturvedi et al 2004, Senanayake et al 2004, Singh et al 1989). Typically, decreases in triglyceride and LDL levels and increases in HDL levels are seen.

In contrast, karela oil increased total lipid levels and phospholipid concentrations in heart and brain as compared with linseed, according to an in vivo study (Dhar & Bhattacharyya 1998).

Antiviral

Several constituents found in bitter melon (e.g. alpha- and beta-momorcharin, lectin and MAP 30) have demonstrated in vitro antiviral activity against Epstein-Barr, HSV-1, HIV, coxsackievirus B3 and polio viruses (Beloin et al 2005, Bourinbaiar & Lee-Huang 1996, Foa-Tomasi et al 1982, Grover & Yadav 2004, Sun et al 2001).

A study using a lyophilised extract of *Momordica charantia* against HSV-1 suggests that the presence of light may be important for antiviral activity (Beloin et al 2005). The active antiviral constituents are not the main bitter principles momordicins I and II, as these have not shown activity against HSV-1 (Beloin et al 2005). One constituent referred to as MAP 30 has received special attention, as it exhibits potent inhibition of HIV-1 and HSV (Schreiber et al 1999).

Antibacterial

Broad-spectrum antibacterial activity has been demonstrated for the leaf extracts (aqueous, ethanol and methanol) (Grover & Yadav 2004). In vitro antimicrobial activity occurred against *Escherichia coli*, *Salmonella paratyphi*, *Shigella dysenterae* and *Streptomyces griseus* (Grover & Yadav 2004, Ogata et al 1991, Omoregbe et al 1996). In a phase II study, the leaf extracts inhibited the growth of *Mycobacterium tuberculosis* in vitro, using the BACTEC 460 susceptibility test method (Frame et al 1998).

Tests with an extract of the entire plant demonstrated antiprotozoal activity against *Entamoeba histolytica* (Grover & Yadav 2004) and a fruit extract exhibited activity against *Helicobacter pylori* (Yesilada et al 1999).

Anti-inflammatory

Bitter gourd extract has been found to suppress lipopolysaccharide (LPS)-induced TNF-alpha production in vitro and, more recently, the butanol-soluble fraction was also found to strongly suppress LPS-induced TNF-alpha production (Kobori et al 2008).

Anthelmintic

The anthelmintic activity of the leaves of *Momordica charantia* against *Caenorhabditis elegans* was identified and described as high in one study (Beloin et al 2005).

Triterpene glycosides of bitter melon (momordicins I and II) were found to be very active nematicides. A preparation of *M. charantia* exhibited stronger anthelmintic activity in vitro than piperazine hexahydrate against *Ascaridia galli* (Lal et al 1976).

Abortifacient

Experimental studies with mice have demonstrated that bitter melon can induce abortions (Chan et al 1984, 1985, Tam et al 1984). According to an in vivo study, the glycoproteins alpha- and beta-momorcharin isolated from the seeds are effective in inducing early and midterm abortions (Chan et al 1986) and the momorcharins were teratogenic in cultured mouse embryos (Chan et al 1986).

OTHER ACTIONS

Anticancer

Various preliminary studies (in vitro and in vivo) with crude bitter melon extract and its various constituents (e.g. MAP 30, momordin I, alpha-momorcharin) have shown anticancer activity (Basch et al 2003).

Analgesic

An in vivo study identified a dose-dependent analgesic effect for a methanolic extract of bitter melon seeds (Biswas et al 1991). The dose that produced a 50% response was 5 mg/kg SC. Analgesic activity was rapid and short lived. The opiate pathway was not involved, as naloxone pretreatment did not modify the analgesic response.

Wound healing

Momordica charantia Linn. fruit powder, in the form of an ointment (10% w/w dried powder in simple ointment base), was evaluated for wound-healing potential in an excision, incision and dead space wound model in rats (Prasad et al 2006). The Momordica ointment produced a statistically significant response ($P < 0.01$), in terms of wound-contracting ability, wound closure time, period of epithelisation, tensile strength of the wound and regeneration of tissues at wound site when compared with the control group. These results were comparable to those of the reference drug used, which was povidone iodine ointment.

CLINICAL USE

Although bitter melon and several of its constituents have been investigated in many experimental studies, few clinical studies have been conducted.

Diabetes

Bitter melon has shown promising effects in prevention as well as delay in progression of diabetic complications (e.g. nephropathy, neuropathy, cataract and insulin resistance) in experimental animals (Grover & Yadav 2004).

Various bitter melon preparations, such as bitter melon fruit juice, dried fruit, seeds and tea have been investigated for hypoglycaemic activity. Some preparations have demonstrated hypoglycaemic activity in clinical studies and experimental models; however, sample sizes are consistently small and statistical analyses are vaguely described (Dans et al 2007).

Most recently, a randomised, double-blind trial was conducted by Dans et al at the outpatient clinic of the Philippines General Hospital (Dans et al 2007). The study involved 40 patients who were either newly diagnosed with type 2 diabetes or had poorly controlled type 2 diabetes. Patients were randomised to receive either *M. charantia* capsules (two capsules three times daily) after meals or placebo as an adjunct to their preexisting medication. HbA_{1c} in both the bitter gourd treatment group and the control group showed a statistically insignificant rise with a mean change of −0.28% and −0.50%, respectively. The mean difference of 0.217 (95% CI: −0.40 to 0.84) was in favour of bitter gourd but did not reach statistical significance ($P = 0.483$). The authors concluded that the study was underpowered and suggested that a larger study with greater numbers is required to better measure any significant changes. The study identified gastrointestinal complaints as the most commonly reported adverse event, in particular abdominal discomfort or pain and diarrhoea.

Cancer

Controlled studies are not available to determine the clinical significance of the encouraging experimental findings.

According to an intriguing case report from the 1970s, a patient with gallbladder carcinoma who was given an estimated survival of 2 years after surgery survived a further 10 years, possibly because of drinking bitter melon tea daily. The signs and symptoms of disease reappeared after consumption of the tea ceased for 4 months because of lack of availability and the patient subsequently died (West et al 1971).

HIV

Nine case reports of people with HIV taking bitter melon, sometimes in combination with other herbal medicines, suggest that it may normalise the CD4/CD8 ratio; however, further investigation is required (Zhang & Khanyile 1992).

OTHER USES

Traditionally, bitter melon has been used as a treatment for a variety of conditions such as diabetes, gastrointestinal complaints, worms, constipation, headaches, skin conditions, viral infections and as an emmenagogue in reproductive health. Experimental studies support its use in some of these indications; however, controlled studies are still required to determine its role in practice.

DOSAGE RANGE

General guide

- Juice: 50–100 mL/day.

According to clinical studies

- Diabetes: aqueous extract of bitter melon fruit juice containing 100 g of fruit in 100 mL of extract taken daily.

ADVERSE REACTIONS

Gastrointestinal symptoms are the most common adverse effects seen. Clinically, this occurs

as epigastric discomfort, pain and diarrhoea which ceases once treatment is stopped.

There are two case reports of bitter melon tea inducing hypoglycaemic coma and convulsions in children (Basch et al 2003). Headaches have been reported with ingestion of the seeds (Ulbricht & Basch 2005).

SIGNIFICANT INTERACTIONS

Controlled studies are not available; therefore, interactions are based on evidence of activity and are largely theoretical and speculative.

Hypoglycaemic agents

Theoretically an additive effect is possible, resulting in increased hypoglycaemic effects — caution. Possible beneficial interaction when used under professional supervision.

CONTRAINDICATIONS AND PRECAUTIONS

Avoid bitter melon seed or the outer rind due to the presence of toxic lectins and avoid use of bitter melon in people with glucose-6-phosphate dehydrogenase deficiency (Ulbricht & Basch 2005).

When low doses of bitter melon extract were ingested for up to 2 months in experimental models, no signs of nephrotoxicity, hepatotoxicity or adverse effects on food intake, growth organ weights and haematological parameters were observed. However, toxicity and even death in laboratory animals have been reported when extracts in high doses were administered intravenously or intraperitoneally (Kusamran et al 1998).

PREGNANCY USE

Based on experimental studies in animal models and traditional use, bitter melon is contraindicated in pregnancy until safety is established.

PATIENTS' FAQs

What will this herb do for me?

According to preliminary research, bitter melon may lower blood glucose levels and aid in the management of diabetes.

When will it start to work?

This is difficult to predict. Diabetics should monitor their blood glucose readings when taking bitter melon.

Are there any safety issues?

Bitter melon is contraindicated in pregnancy and people with glucose-6-phosphate dehydrogenase deficiency. The seeds and outer rind should be avoided because they contain toxic lectins. Diabetic patients should monitor their blood glucose when taking bitter melon to prevent hypoglycaemia.

PRACTICE POINTS/PATIENT COUNSELLING

- Bitter melon is used as a traditional remedy for diabetes mellitus. Evidence from experimental studies and case reports support moderate hypoglycaemic activity; however, large-scale clinical trials are needed before clinical significance can be clarified.
- Traditionally, bitter melon has also been used as a treatment for gastrointestinal complaints, worms, constipation, headaches, skin conditions, viral infections and as an emmenagogue.
- According to experimental studies, bitter melon and/or its various constituents exert lipid-lowering, antibacterial, anthelmintic, abortifacient, antineoplastic and analgesic activities.
- Bitter melon is contraindicated in pregnancy and people with glucose-6-phosphate dehydrogenase deficiency.
- Avoid bitter melon seed or the outer rind, which have toxic lectins.

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Black cohosh

HISTORICAL NOTE Native Americans first used black cohosh many centuries ago, mainly as a treatment for female reproductive problems, including pain during childbirth, uterine colic and dysmenorrhoea, and also for fatigue, snakebite and arthritis. It was widely adopted by European settlers, eventually becoming a very popular treatment in Europe for gynaecological conditions.

COMMON NAME
Black cohosh

OTHER NAMES
Baneberry, black snakeroot, bugbane, rattle-root, rattle-top, rattleweed, squawroot, traubensilberkerze, wanzenkraut

BOTANICAL NAME/FAMILY
Cimicifuga racemosa now known as *Actaea racemosa* Linnaeus (family Ranunculaceae)

PLANT PARTS USED
Rhizome and root

CHEMICAL COMPONENTS

Black cohosh contains various triterpene glycosides, including cimicifugoside and actein, 27-deoxyactein, *N*-methylcytosine and other quinolizidine alkaloids, phenolic acids, isoferulic and salicylic acids, resins, fatty acids and tannins.

Until recently, the isoflavone, formononetin, was believed to be a pharmacologically important constituent of the herb; however, recent testing of numerous samples has failed to detect it in any sample, including the commercial products Remifemin (Schaper & Brummer GmbH & Co. KG, Salzgitter, Germany) and CimiPure (Kennelly et al 2002).

MAIN ACTIONS

Hormone modulation

The hormonal effects of black cohosh are believed to be the result of complex synergistic actions of several components, particularly the triterpene glycosides. It appears unlikely that black cohosh exerts oestrogenic activity, as although oestrogenic activity has been detected in some tests (Duker et al 1991, Kruse et al 1999, Liu et al 2001), it has not been observed in others (Beck et al 2003, Einer-Jensen et al 1996, Zierau et al 2002). Additionally, the herb has demonstrated anti-oestrogenic activity (Zierau et al 2002).

It has been shown that black cohosh decreases local oestrogen formation in normal human breast tissue in vitro. This may contribute to the lack of hormonal effects of black cohosh in breast tissue observed in previous studies (Stute et al 2007). Preclinical studies to determine how black cohosh works have yielded conflicting results, but several hypotheses have been proposed. It acts either (1) as a selective oestrogen receptor modulator (SERM), (2) through serotonergic pathways, (3) as an antioxidant, or (4) on inflammatory pathways (Ruhlen et al 2008). One study suggests that black cohosh works as a SERM, augmented by central nervous effects (Viereck et al 2005). Results from studies found that it has SERM activity with a lower potency but comparable efficacy to that of 17 beta-oestradiol (Bolle et al 2007). It has no action in the uterus, but beneficial effects in the hypothalamo-pituitary unit and in bone (Seidlova-Wuttke et al 2003). This has been confirmed in a double-blind, randomised, multicentre study (Wuttke et al 2003). In that study, the standardised black cohosh extract BNO 1055 was equipotent with conjugated oestrogens in reducing menopausal symptoms, had beneficial effects on bone metabolism and significantly increased vaginal superficial cells; however, it did not exert uterotrophic activity.

Overall, it is generally agreed that black cohosh reduces LH secretion. This has been confirmed in a human study and is believed to be the result of at least three different active constituents acting synergistically (Duker et al 1991).

Anti-inflammatory

Animal studies have identified some anti-inflammatory activity (Hirabayashi et al 1995).

> ***Clinical note — Selective oestrogen receptor modulators (SERMs)***
>
> These are compounds that, in contrast to pure oestrogen agonists or antagonists, have a mixed and selective pattern of oestrogen agonist–antagonist activity, which largely depends on the tissue targeted. The therapeutic aim of using these substances is to produce oestrogenic actions in those tissues in which it would be beneficial (e.g. bone, brain, liver) and have either no activity or antagonistic activity in tissues, such as breast and endometrium, where oestrogenic actions (like cellular proliferation) might be deleterious. They are a relatively new class of pharmacologically active agents and are being used by women who cannot tolerate pharmaceutical HRT or are unwilling to use it. The most actively studied SERMs are tamoxifen and raloxifen (Hernandez & Pluchino 2003).

Serotonergic

In vitro tests identified compounds in a black cohosh methanol extract that were capable of strong binding to the 5-HT(1A), 5-HT(1D), and 5-HT(7) receptor subtypes (Burdette et al 2003). Further investigation by these authors found that the components functioned as a partial agonist of the 5-HT(7) receptor.

Dopaminergic

It is suggested that the effects of *A. racemosa* may be due to dopaminergic activity, because black cohosh extract BNO 1055 displayed dopaminergic activity with a D(2)-receptor assay (Jarry et al 2003). Considering that dopaminergic drugs reduce some symptoms (e.g. hot flushes) associated with menopause, this theory is feasible; however, further studies are required to explain why black cohosh is devoid of the typical side effects associated with dopaminergic drugs (Borrelli & Ernst 2002).

OTHER ACTIONS

A dose-dependent antihypertensive effect was identified for a triterpene found in black cohosh (actein) in animal tests. The clinical significance of this finding for humans using black cohosh root is unknown (Genazzani & Sorrentino 1962).

Black cohosh is traditionally thought to act as a tonic and nervous system restorative medicine and exert antispasmodic and anti-inflammatory activity.

No effect on CYP3A was detected in a recent human study (Gurley et al 2006a).

CLINICAL USE

Menopausal symptoms

Most clinical research on black cohosh is on its ability to treat menopausal symptoms. Most trials test the commercial preparation of black cohosh known as Remifemin, which is standardised to contain triterpene glycosides (0.8–1.2 mg/tablet), but recently there has been some investigation of BNO 1055, an aqueous ethanolic extract (58% vol/vol), sold as

Klimadynon and Menofem (Bionorica AG, Neumarkt, Germany). Overall, results from clinical studies have been positive but not always consistent making it difficult to reach a definitive conclusion about efficacy. This is likely due to variations in test dose, extraction method, constituent levels present, plant type, and co-administration of other herbs or methodological issues such as variations in outcome measures and small sample size.

A review of eight clinical trials published in 1998 found that black cohosh (Remifemin) is a safe and effective alternative to HRT for menopausal patients in whom HRT is contraindicated (Lieberman 1998). Symptoms responding to treatment with black cohosh included hot flushes, vaginal thinning and drying, night sweats, sleep disturbances, anxiety and depression. Since then there have been a number of clinical trials showing positive benefit for reduction of hot flushes in menopausal women using black cohosh. A pilot study demonstrated that BNO 1055 is able to reduce oestrogen deficiency symptoms to the same degree as conjugated oestrogens (Wuttke et al 2006b). A randomised, double-blind, controlled 3-month study to investigate the efficacy–safety balance of black cohosh (Remifemin) in comparison with tibolone in 244 symptomatic menopausal Chinese women gave remarkable results. The efficacy of both treatments was similar and statistically significant. The safety for both groups was also good. However, the tolerability profile was greatly in favour of the herbal treatment with a significantly lower incidence of adverse events (Bai et al 2007). In a large study of changes in subjective symptoms of menopause in 2016 Hungarian women black cohosh was found to be effective in the alleviation of menopausal symptoms, especially reduction of hot flushes (Vermes et al 2005). In another prospective study, hot flushes and night sweats decreased to a greater extent in women taking black cohosh compared with fluoxetine (Oktem et al 2007). Black cohosh had a significant effect in women with menopausal disorders of moderate intensity decreasing scores on the Menopause Rating Scale by 48% compared with 14% for placebo according to a randomised, placebo-controlled, double-blind study (Frei-Kleiner et al 2005). Another double-blind, randomised, multicentre study compared the effects of BNO 1055 (40 mg/d) to conjugated oestrogens (0.6 mg/d) and placebo on climacteric complaints, bone metabolism and endometrium (Wuttke et al 2003). The study involved 62 postmenopausal women who took their allocated treatment for 3 months. BNO 1055 proved to be equipotent to conjugated oestrogens and superior to a placebo in reducing climacteric symptoms, and both active treatments produced beneficial effects on bone metabolism. Vaginal superficial cells increased with both active treatments; however, BNO 1055 had no effect on endometrial thickness, which was significantly increased by conjugated oestrogens.

Two RCTs found stronger effects of black cohosh in perimenopausal than in postmenopausal women (Frei-Kleiner et al 2005, Osmers et al 2005). Preclinical studies have suggested that a combination of oestrogen and black cohosh is more effective than oestrogen alone. Therefore, the efficacy of black cohosh could be enhanced by the presence of endogenous oestradiol that still occurs in perimenopausal women.

There have been a couple of notable exceptions to these positive findings. A large randomised controlled study (n = 351) of herbal alternatives for menopause, the HALT study, which tested black cohosh, a multibotanical (including 200 mg of black cohosh), a multibotanical plus soy diet counselling, oestrogen ± progesterone, and placebo found that there were no statistically significant differences in the average adjusted change in vasomotor symptoms per day or in vasomotor symptom intensity between the herbal interventions and placebo at 3, 6 or 12 months (Newton et al 2006). The HALT study also showed that black cohosh had no demonstrable effects on lipids, fibrinogen, glucose and insulin (Spangler et al 2007). A smaller double-blind, randomised, crossover clinical trial also failed to provide any evidence that black cohosh reduced hot flushes beyond placebo treatment (Pockaj et al 2006).

Given the number of clinical trials and the conflicting evidence on efficacy of black cohosh in alleviating menopausal symptoms, there have been a number of systematic reviews of the evidence. One systematic review, including randomised, controlled trials, open trials and comparison group studies, found that the evidence to date suggests that black cohosh is safe and effective for reducing menopausal symptoms, primarily hot flushes and possibly mood disorders (Geller & Studee 2005). Later reviews by the same research team showed that black cohosh significantly reduced depression and anxiety in all studies reviewed (Geller & Studee 2007). Another more recent systematic review identified seven randomised controlled trials of black cohosh and concluded that it may be beneficial in the treatment of menopausal vasomotor symptoms in some women (Cheema et al 2007).

An update of a previous systematic review evaluated the clinical evidence for or against the efficacy of black cohosh in alleviating menopausal symptoms. Seventy-two clinical trials were identified but only six of these, with a total of 1163 peri and postmenopausal women, met the inclusion criteria. With one exception, the results for each of these trials were positive; yet, the authors concluded that the efficacy of black cohosh in reducing menopause symptoms is currently not supported by full conclusive evidence, citing small sample size as a limitation in establishing statistical significance (Borrelli & Ernst 2008). Similarly, a recent review of 16 eligible studies suggested that there were methodological flaws in many studies making a definitive conclusion difficult. Methodological issues included: lack of uniformity of the drug preparation used, variable outcome measures and lack of a placebo group (Palacio et al 2009). Clearly, further investigation is required to clarify the most effective preparation and method of use for black cohosh in the treatment of menopausal symptoms.

Weight gain

Rat models demonstrate that BNO 1055 black cohosh extract decreases enhanced pituitary LH secretion, attenuates body weight gain and intra-abdominal fat accumulation, lowers fasting plasma insulin and has no effects on uterine mass. The effects on plasma lipids are complex and are characterised by an increase of LDL cholesterol and decrease of triglyceride levels, which is in contrast to the effects of oestrogen (Rachon et al 2008). There has been no investigation of these effects in human trials.

Osteoporosis prevention

Black cohosh demonstrates osteoprotective effects comparable to oestrogen, although through a different mechanism of increasing osteoblast activity (Wuttke et al 2006a), mediated via an oestrogen receptor-dependent mechanism (Chan et al 2008). A recent experimental study has shown that a triterpenoid glycoside isolated from black cohosh (25-acetyl-cimigenol xylopyranoside) both blocks the osteoclastogenesis enhanced by cytokines in vitro and attenuates TNF-alpha-induced bone loss in vivo (Qiu et al 2007). These results demonstrate that black cohosh can offer effective prevention of postmenopausal bone loss.

Breast cancer protection

A number of in vitro studies on black cohosh show that it is cytotoxic to human breast cancer cells and inhibits the conversion of oestrone sulphate to active oestradiol in breast cancer cells (Rice et al 2007), and suppresses tumour cell invasion without affecting cell viability (Hostanska et al 2007). One in vitro study found that black cohosh enhances the action of some chemotherapy agents, most notably tamoxifen (Al-Akoum et al 2007). The triterpene glycoside, actein, induced a stress response and apoptosis in human breast cancer cells (Einbond et al 2006, 2007, 2008). A recent in vitro study suggests that a herbal combination, Avlimil (which includes black cohosh, licorice, red raspberry, red clover and kudzu), exhibits both stimulatory and inhibitory effects on the growth of oestrogen-dependent breast tumour (MCF-7) cells. This casts doubt on the safety of Avlimil for women with oestrogen-dependent breast cancer (Ju et al 2008).

A randomised study (Hernandez & Pluchino 2003) was also performed with 136 young premenopausal breast cancer survivors experiencing hot flushes as a result of tamoxifen therapy. When BNO 1055 (Menofem/Klimadynon, corresponding to 20 mg of herbal drug) was used together with tamoxifen for 12 months, the number and severity of hot flushes were reduced, with almost 50% of subjects becoming free of hot flushes, and severe hot flushes were reported by only 24% compared with 74% for those using tamoxifen alone.

In contrast, a previous double-blind, placebo-controlled study (n = 85) failed to detect significant improvements with black cohosh for hot flush frequency or severity when used by patients with breast cancer for 2 months and who were also taking tamoxifen (Jacobson et al 2001). Unfortunately, the authors of that study did not specify which black cohosh product was being used or the dosage, making a comparison with the previous study difficult.

Herbal combination studies

A number of studies have been conducted investigating the combination of black cohosh and St John's wort for the treatment of symptoms of menopause with mood symptoms. One double-blind, randomised study of 301 women found that 16 weeks of herbal treatment produced a significant 50% reduction in the Menopause Rating Scale score compared with 20% with placebo and a significant 42% reduction in the Hamilton Depression Rating Scale compared with only 13% in the placebo group (Uebelhack et al 2006). Another large-scale (n = 6141), prospective, controlled open-label observational study supports the effectiveness and tolerability of black cohosh combined with St John's wort for alleviating menopausal mood symptoms (Briese et al 2007). In another double-blind, randomised, placebo-controlled, multicentre study, 89 peri or postmenopausal women experiencing menopause symptoms were treated with a combination of St John's wort and black cohosh extract (Gynoplus) or a matched placebo. Hot flushes were significantly lower and HDL levels increased in the Gynoplus group (Chung et al 2007).

A combination of soy isoflavones, black cohosh and nutritional supplements failed to have a significant effect on menopausal symptoms in a 12-week randomised, placebo-controlled, double-blind study of 124 women (Verhoeven et al 2005).

Commission E has approved the use of this herb as a treatment for menopausal symptoms (Blumenthal et al 2000). Similarly, the World Health Organization (WHO) recognises its use for the 'treatment of climacteric symptoms such as hot flushes, profuse sweating, sleeping disorders and nervous irritability'. The North American Menopause Society recommends black cohosh, in conjunction with lifestyle approaches, as a treatment option for women with mild menopause-related symptoms (North American Menopause Society 2004). In herbal practice generally, menopausal symptoms are usually addressed using a combination of herbs, supplements and dietary and lifestyle advice.

Premenstrual syndrome and dysmenorrhoea

Commission E has approved the use of black cohosh as a treatment in these conditions (Blumenthal et al 2000). Randomised clinical studies are still required to confirm efficacy in these conditions.

Menstrual migraine

An RCT of 49 women with menstrual migraines tested placebo against a herbal combination consisting of 60 mg soy isoflavones, 100 mg dong quai and 50 mg black cohosh, with each component standardised to its primary alkaloid (Burke et al 2002). Over the course of the study, the average frequency of menstrually associated migraine episodes was significantly reduced in the active treatment group.

OTHER USES

Prostate cancer

Two in vitro studies suggest that black cohosh may have theoretical usefulness in the treatment of prostate cancer (Hostanska et al 2005, Jarry et al 2005, Seidlova-Wuttke et al 2006). Further research may demonstrate that black cohosh can effectively prevent and treat prostate cancer.

Black cohosh has been used traditionally to treat a variety of other female reproductive disorders, inflammatory disorders, especially menopausal arthritis and diarrhoea. It has also been used to promote menstruation. The British Herbal Pharmacopoeia states it is indicated in ovarian dysfunction and ovarian insufficiency.

SAFETY

Four hundred postmenopausal women with symptoms related to oestrogen deficiency were enrolled into a prospective, open-label, multinational, multicentre study to investigate endometrial safety and the tolerability and efficacy of the black cohosh extract, BNO 1055. Low dose treatment (40 mg) for 52 weeks showed no case of hyperplasia or more serious adverse endometrial outcome occurred (Raus et al 2006). This finding is supported by the HALT study (Reed et al 2008).

A population-based case-control study consisting of 949 breast cancer cases and 1524 controls was used to evaluate the relationship between phytoestrogens and breast cancer risk. Use of black cohosh was found to have a significant breast cancer protective effect. This association was similar among women who reported use of either black cohosh or Remifemin (Rebbeck et al 2007). Another smaller trial demonstrated that Remifemin does not cause adverse effects on breast tissue. A total of 65 healthy, naturally postmenopausal women completed a trial with 40 mg black cohosh daily. Mammograms were performed, and breast cells were collected by percutaneous fine needle aspiration biopsies at baseline and after 6 months (Hirschberg et al 2007). A systematic review was conducted about the safety and efficacy of black cohosh in patients with cancer. There is laboratory evidence of antiproliferative properties but no confirmation from clinical studies for a protective role in cancer prevention. Black cohosh appears to be safe in breast cancer patients (Walji et al 2007).

A pharmacoepidemiologic, observational, retrospective cohort study examined breast cancer patients to investigate the influence of Remifemin on recurrence-free survival after breast cancer, including oestrogen-dependent tumours. Remifemin was not found to be associated with an increase in the risk of recurrence but was associated with prolonged disease-free survival. After 2 years following initial diagnosis, 14% of the control group had developed a recurrence, while the Remifemin group reached this proportion after 6.5 years, demonstrating a protractive effect of black cohosh on the rate of recurrence of breast cancer for women with a history of breast cancer who had used Remifemin, compared to women who had not (Zepelin et al 2007).

DOSAGE RANGE

- Decoction or powdered root: 0.3–2 g three times daily.
- Tincture (1:10): 2–4 mL three times daily.
- Fluid extract (1:1) (g/mL): 0.3–2 mL three times daily.

Many practitioners have used black cohosh long term without safety concerns; however, Commission E does not recommend more than 6 months' continuous use.

TOXICITY

Overdose has produced nausea and vomiting, vertigo and visual disturbances.

Idiosyncratic hepatic reactions

Rare, spontaneous hepatotoxicity has been reported in 42 case reports world-wide with treatment by *Cimicifugae racemosae rhizoma* (Levitsky et al 2005, Lynch et al 2006, Nisbet & O'Connor 2007, Teschke & Schwarzenboeck 2009, Whiting et al 2002). As a result, several safety reviews have been conducted to evaluate the available data and determine what risk exists with the use of this herb. A safety review of black cohosh products was recently conducted by the Dietary Supplement Information Expert Committee of the US Pharmacopeia's Council of Experts. All the reports of liver damage were assigned possible causality, and none were probable or certain causality. The clinical pharmacokinetic and animal toxicological information did not reveal unfavourable information about black cohosh. The Expert Committee determined that in USA black cohosh products should be labelled to include a cautionary statement, a change from their decision of 2002, which required no such statement (Mahady et al 2008).

Assessment of the 42 cases by European Medicines Agency (EMEA) has shown a possible or probable causality in only four out of 42 patients. A diagnostic algorithm has been applied in the four patients with suspected BC hepatotoxicity using several methods to allow objective assessment, scoring and scaling of the probability in each case. Due to incomplete data, the case of one patient was not assessable. For the remaining three patients, quantitative evaluation showed no causality for BC in any patient regarding the observed severe liver disease (Teschke & Schwarzenboeck 2009).

In Australia in February 2006, the TGA announced that based on the appraisal of case reports, a causal association between black cohosh and serious hepatitis exists; however, the incidence is very low considering its widespread use. As a result, products available in Australia containing black cohosh have to carry label warnings informing consumers of the risk. The conclusion made by the TGA is considered controversial by some experts because numerous confounding factors were present in many of the case reports, such as the use of multiple ingredient preparations, concurrent use of at least one pharmaceutical medicine and the presence of other medical conditions.

A recent study evaluated the effects of black cohosh extract on liver morphology and on levels

of various hepatic function indices in an experimental model finding that at high doses, well above the recommended dosage, black cohosh appears quite safe (Mazzanti et al 2008).

ADVERSE REACTIONS

Although large doses are reported to produce, headache, tremors or giddiness in some people, gastrointestinal disturbances and rashes are the most common adverse effects, according to data from clinical studies and spontaneous reporting programs (Huntley & Ernst 2003). A few serious adverse events, including hepatic and circulatory conditions, have been reported, but without a clear causality relationship (see above). Two cases of cutaneous vasculitis were tenuously linked to supplementation with black cohosh (Ingraffea et al 2007), although no analysis was undertaken to determine specifically what ingredients the supplement contained. One case of pseudolymphoma was linked to Remifemin, which the patient had taken for 1 year. Six months after initial administration of Remifemin skin lesions appeared which continuously increased. Withdrawal of Remifemin resulted in regression and complete remission of the lesions within 12 weeks (Meyer et al 2007). In another case, a woman with severe asthenia and very high blood levels of creatine phosphokinase and lactate dehydrogenase showed a progressive normalisation of biochemical parameters and improvement of myopathy after discontinuing a dietary supplement derived from black cohosh (product not specified). A causative role for black cohosh was hypothesised because of the temporal relationship between use of herbal product and asthenia and the absence of other identified causative factors. Rechallenge with the suspected agent was inadvisable for ethical reasons because of the risk of a serious relapse (Minciullo et al 2006). Both these adverse events are likely to be the result of idiosyncratic reaction to black cohosh.

Despite these reports, the adverse effects of black cohosh tend to be rare, mild and reversible.

SIGNIFICANT INTERACTIONS

A human trial examined the use of a black cohosh (40 mg daily) supplement for 14 days to test phytochemical-mediated modulation of P-glycoprotein (P-gp) and other drug transporters thought to underlie many herb–drug interactions. No statistically significant effects on digoxin pharmacokinetics were observed following supplementation with black cohosh indicating no effect on P-gp (Gurley et al 2006b).

Cisplatin

Black cohosh decreased the cytotoxicity of cisplatin in an experimental breast cancer model — whilst the clinical significance of this finding is unknown, it is recommended that patients taking cisplatin should avoid black cohosh until safety can be confirmed.

Doxorubicin

Black cohosh increased the cytotoxicity of doxorubicin in an experimental breast cancer model — whilst the clinical significance of this finding is unknown, it is recommended patients taking doxorubicin avoid black cohosh until safety can be confirmed.

Docetaxel

A trial used mouse breast cancer cell line to test whether black cohosh altered the response of cancer cells to radiation and to four drugs commonly used in cancer therapy. The black cohosh extracts increased the cytotoxicity of doxorubicin and docetaxel and decreased the cytotoxicity of cisplatin, but did not alter the effects of radiation or 4-hydroperoxycyclophosphamide (4-HC), an analogue of cyclophosphamide which is active in cell culture. This evidence may be applicable to humans so it is advisable that patients undergoing cancer therapy should be made aware that use of black cohosh could alter their response to the agents commonly used to treat breast cancer (Rockwell et al 2005).

CONTRAINDICATIONS AND PRECAUTIONS

There is some controversy over the use of black cohosh in women with a history of breast cancer. Results from a 2002 study testing the safety of black cohosh in an in vitro model for oestrogen-dependent breast tumours found that the herbal extract significantly inhibited tumour cell proliferation, oestrogen-induced proliferation and enhanced the antiproliferative effects of tamoxifen (Bodinet & Freudenstein 2002). This finding is supported in a more recent in vitro study which showed black cohosh having a cytotoxic effect on both oestrogen-sensitive and oestrogen-insensitive breast cancer cells and a synergism with tamoxifen for inhibition of cancerous cell growth (Al-Akoum et al 2007). The synergistic action of black cohosh and tamoxifen needs to be taken into account and evidence that oestrogenic action may not be clinically relevant. Despite this positive preliminary evidence, no clinical studies are available to help establish safety in women with a history of breast cancer. As a result, it is suggested that black cohosh only be used under professional supervision in people with oestrogen-dependent tumours.

PREGNANCY USE

Although it has been used to assist in childbirth, black cohosh is not traditionally recommended in pregnancy, particularly during the first trimester although it has been used in the final weeks of pregnancy to aid in delivery. Safety in lactation remains to be confirmed; however, it is usually avoided because of its hormonal effects (Dugoua et al 2006).

PATIENTS' FAQs

What will this herb do for me?

Black cohosh may be an effective treatment for menopausal symptoms in most women, especially those with mild to moderate symptoms. It may also be useful in the treatment of premenstrual syndrome and prevention of period cramping.

When will it start to work?

Studies suggest that benefits are seen within 4–12 weeks for the treatment of menopausal symptoms.

Are there any safety issues?

Black cohosh should only be used under professional supervision by people undergoing chemotherapy, receiving treatment for oestrogen-dependent tumours or during pregnancy.

PRACTICE POINTS/PATIENT COUNSELLING

- In general, clinical trials support the use of black cohosh for menopausal symptoms; however, not all studies have yielded consistent results and further research is indicated to provide definitive proof.
- It appears that 4–12 weeks' continuous treatment are required for adequate menopausal symptom relief.
- Black cohosh is also used in the treatment of premenstrual syndrome and dysmenorrhoea and is Commission E-approved for these uses; however, controlled studies are not available to confirm its efficacy.
- There is some evidence suggesting that black cohosh exerts selective oestrogen receptor modulator activity, serotonergic activity and possibly dopaminergic activity.
- Black cohosh should be used only under professional supervision by people with oestrogen-dependent tumours or during pregnancy.
- Black cohosh is well tolerated; however, rare case reports of idiosyncratic hepatic reactions have been described.

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Brahmi

HISTORICAL NOTE Brahmi is the Sanskrit name for the herb *Bacopa monniera* and has been used in Ayurvedic medicine as a nerve tonic since time immemorial. Under this system, *B. monniera* is classified under 'Medhya rasayana', that is, medicinal plants rejuvenating intellect and memory and has been used in India for almost 3000 years. The ancient classical Ayurvedic treatises recommend it for the promotion of memory, intelligence and general performance. Over time, it has earned a reputation as an important brain tonic (Williamson 2002).

COMMON NAME
Brahmi

OTHER NAMES
Bacopa, herb of grace, herpestis herb, Indian pennywort, jalanimba, jalnaveri, sambrani chettu, thymeleave gratiola, keenmind, Nira-Brahmi, Sambrani Chettu

Centella asiatica (gotu kola) and *Merremia gangetica* have also been referred to by the name brahmi, but most authorities associate brahmi with *Bacopa monniera*. The name Brahmi is derived from the word 'Brama', the mythical 'creator' in the Hindu pantheon. Because the brain is the centre for creative activity, any compound that improves the brain health is called Brahmi (Russo & Borrelli 2005).

BOTANICAL NAME/FAMILY
Bacopa monniera (family Scrophulariaceae)

PLANT PARTS USED
Dried whole plant or herb, mainly leaves and stems (aerial parts)

CHEMICAL COMPONENTS
Dammarene-type saponins (bacosides (A, B, C) and bacosaponines (D, E, F), based on the bacogenins A1–A5, are considered the most important) and alkaloids (brahmine, herpestine), flavonoids (luteolin-7-glucoside, glucuronyl-7-apigenin and glucuronyl-7-luteolin), phytosterols (Chakravarty et al 2003) and luteolin, phenylethanoid glycosides, monnierasides I–III and plantainoside B have been isolated (Adams et al 2007).

Standardised extract BacoMind™ has been shown to contain bacoside A_3, bacopaside I, bacopaside II, jujubogenin isomer of bacopasaponin C, bacosine, luteolin, apigenin and β-sitosterol D glucoside (Dutta et al 2008).

MAIN ACTIONS
The mechanism of action of brahmi has not been significantly investigated in clinical studies, so results from in vitro and animal tests provide most of the mechanistic evidence. Some studies have investigated the effects of an Ayurvedic herbal combination known as brahmi rasayan, which consists of 10 parts bacopa, 2 parts cloves, 1 part cardamom, 1 part *Piper longum* and 40 parts sucrose.

Antioxidant
Brahmi has potent antioxidant activity, which appears to be a result of both direct free-radical scavenging activity and increasing the activity of endogenous antioxidant systems (Bhattacharya et al 2000, Tripathi et al 1996). Administration of bacoside A reduced the effects of cigarette smoke in an animal model by increasing lactate dehydrogenase and its isoenzymes (Anbarasi et al 2005a). Bacoside A has also been shown to reduce creatine kinase in brain and cardiac tissue (Anbarasi et al 2005b), and prevent expression of hsp70 and neuronal apoptosis (Anbarasi et al 2006) thus preventing smoke-induced damage. An extract of brahmi provided protection against DNA damage in both animal cells (Russo et al 2003a) and human cells (Russo et al 2003b) in vitro. Dose-related increases in superoxide dismutase, catalase and glutathione peroxidase activities in several important regions of the brain has been demonstrated in animal models (Bhattacharya et al 2000) and it has been shown to induce the activity of superoxide dismutase and catalase in the liver (Kar et al 2002). Additionally, brahmi enhances antioxidant activity to protect against reactive oxygen species (ROS)-induced damage in diabetic rats (Kapoor et al 2009).

Neuroprotective
Bacopa has demonstrated neuroprotective activity in a number of animal models, chiefly mediated by an antioxidant mechanism. In one study, bacopa significantly protected lipids and proteins from oxidative stress-induced damage caused by aluminium. The protective antioxidant effect was described as similar to L-deprenyl (Jyoti et al 2007).

In another experiment, bacopa improved memory functions in hypobaric conditions which induce hypoxia, most likely due to neuroprotective activity, antioxidant and mitochondria stabilising effects (Hota et al 2009).

Administration of bacoside A prevented the structural and functional impairment of mitochondria upon exposure to cigarette smoke in vivo (Anbarasi et al 2005c). From the results, it was suggested that chronic cigarette smoke exposure induces damage to the mitochondria and that bacoside A protects the brain from this damage by maintaining the structural and functional integrity of the mitochondrial membrane.

In an Alzheimer's dementia model, bacopa extract significantly reduced beta-amyloid levels when administered prior to beta-amyloid deposition (Dhanasekaran et al 2004). The neuroprotective effect was specific for beta amyloid-induced cell death but not glutamate-induced excitotoxicity (Limpeanchob et al 2008). Bacopa extracts contain polyphenols and sulfhydryl compounds that

demonstrate dose-dependent antioxidant activity, which reduces divalent metals, decreases the formation of lipid peroxides and inhibits lipoxygenase activity (Dhanasekaran et al 2007).

Cognitive or nootropic effects

Evidence shows that the effects on the cholinergic system include the modulation of acetylcholine release, choline acetylase activity and muscarinic cholinergic receptor binding (Das et al 2002). Cholinergic effects in combination with antioxidant and mitochondrial stabilisation effects are suggested as the mechanisms responsible for cognitive activation. Results from a double-blind, placebo-controlled trial using brahmi (300 mg/d) support this view, as one of the major effects seen was on speed of early information processing, a function predominantly modulated by the cholinergic system (Stough et al 2001). More recently, *Bacopa monniera* (120 mg/kg oral) significantly reversed diazepam-induced (1.75 mg/kg i.p.) amnesia in an animal study (Saraf et al 2008) thereby confirming previous reports of cholinergic activity (Dhanasekaran et al 2007). The saponins bacoside A and B are considered to be the most important active constituents responsible for enhancing cognitive function (Russo et al 2005, Singh & Dhawan 1982).

Antidepressant activity

A rodent model of depression found that an extract of brahmi produced significant antidepressant activity comparable to that of imipramine after 5 days of oral administration (Sairam et al 2002).

Antiulcer effects

Significant antiulcer activity for the fresh juice from the whole plant of *Bacopa monniera* has been demonstrated in an animal model of aspirin-induced gastric ulceration (Rao et al 2000). The study found that brahmi had a beneficial influence on the natural mucosal defensive factors, such as enhanced mucin secretion, mucosal glycoprotein production and decreased cell shedding, thereby reducing ulceration (Rao et al 2000). A follow-up in vivo study in various gastric ulcer models further confirmed brahmi's ability to increase the body's natural defence factors and showed that *B. monniera* is effective for both the prophylaxis and treatment of gastric ulcers (Sairam et al 2001). In addition, brahmi was shown to reduce lipid peroxidation. An in vitro study demonstrated that *B. monniera* significantly inhibited *Helicobacter pylori*, and the effect was comparable to that of bismuth subcitrate, a known *H. pylori* growth inhibitor (Goel et al 2003).

Anti-inflammatory effects

Several different mechanisms are responsible for the observed anti-inflammatory activity of brahmi. Inhibition of COX-2, 5-LOX and 15-LOX and down regulation of TNF-alpha was demonstrated in one study testing a methanolic extract of *B. monniera*. The activity was found for both EtOAc and bacoside fractions (Viji & Helen 2008). Channa et al (2006) also identified anti-inflammatory activity but reported that this was mediated by PGE_2 inhibition, inhibition of histamine, serotonin and bradykinin release (Channa et al 2006).

The anti-inflammatory activity of bacopa was found to be comparable to indomethacin without causing an associated gastric irritation (Jain et al 1994). Several constituents are thought to be responsible for the anti-inflammatory action, chiefly the triterpene, betulinic acid, saponins and flavonoids.

OTHER ACTIONS

Adaptogen

A standardised extract of *B. monniera* possesses adaptogenic effects in an animal model, which were found to be comparable to *Panax quinquefolium* (Rai et al 2003). The neuropharmacological adaptogenic activity of brahmi was identified by significant normalisation of stress-induced changes in plasma corticosterone, and monoamine levels and dopamine in cortex and hippocampus regions of the brain (Sheikh et al 2007).

Antinociceptive activity

Brahmi rasayan (an Ayurvedic herbal combination containing brahmi) has demonstrated antinociceptive activity in animal experiments (Shukia et al 1987). An interaction with the GABA-ergic system is believed to be involved. Although encouraging, it is not certain to what extent brahmi was responsible for these results.

Mast cell stabilisation

The methanolic fraction of brahmi exhibits potent mast cell stabilising activity in vitro, which was found to be comparable to that of disodium cromoglycate (Samiulla et al 2001).

Increased thyroid hormone levels

Results from animal experiments have found that brahmi increases T_4 concentrations by 41% without enhancing hepatic lipid peroxidation (Kar et al 2002).

Antispasmodic effect on smooth muscle

A spasmolytic effect on smooth muscle has been demonstrated in vivo, and is predominantly due to inhibition of calcium influx into the cell (Dar & Channa 1999). Bronchodilatory effects have also been demonstrated, most likely due to the same mechanism (Channa et al 2003).

Anticlastogenic effect

An in vitro study identified significant anticlastogenic effects of the standardised extract of BacoMind™ on human lymphocytes due to the herb's antioxidant activity (Dutta et al 2008).

Hepatoprotective

Bacoside A was hepatoprotective against D-galactosamine-induced liver injury in rat studies. Researchers found that bacoside A reduced ALT, AST, ALP, γ-GT, LDH and 5'ND enzyme levels and restored the decreased levels of vitamins C and E reduced by D-galactosamine in both liver and plasma (Sumathi & Nongbri 2008).

Clinical note — Scientific investigation of Ayurvedic medicines in India

Modern-day interest in many Ayurvedic herbs, such as brahmi, really started in 1951 when the then Prime Minister of India set up the Central Drug Research centre in Lucknow. The goal of this initiative was to encourage scientists to investigate many of the traditional Ayurvedic herbs in a scientific way, and to determine their potential as contemporary drugs or as potential sources for newer drugs.

CLINICAL USE

Brahmi has been subject to many in vitro and animal studies, which indicate that the herb and several of its key constituents have significant pharmacological activity. Increasingly, clinical studies are being published; however, there is much that remains untested, so information derived from preliminary scientific evidence and traditional evidence is still used as a basis for some clinical applications.

Improving cognitive function — learning, memory, intelligence

In Ayurvedic medicine, bacopa is used to improve cognitive function and increase intelligence. Over time, it has developed an excellent reputation, prompting scientific researchers to investigate the activity of bacopa more closely.

To date, results from animal studies and human trials are encouraging and generally positive; however, more high-quality studies are required. Oral administration of brahmi extract (40 mg/kg) for at least 3 days produced positive effects on learning skills, memory and reaction times compared with controls in one learning model (Singh & Dhawan 1982). Another study found that bacopa extract significantly reversed the cognitive impairment induced by the antiepileptic drug phenytoin, without affecting its anticonvulsant activity (Vohora et al 2000). More recent animal studies have shown that bacopa attenuates hyoscine-induced dementia and significantly inhibits acetylcholinesterase activity in vitro (Das et al 2002). Studies indicate that bacosides A and B present in the ethanolic extract are responsible for the cognition facilitating effects (Russo 2005).

Clinical studies have generally produced encouraging results. A double-blind, placebo-controlled trial using a dose of 300 mg bacopa over 12 weeks in 46 healthy volunteers found that it significantly improved the speed of visual information processing, learning rate and memory consolidation and that it has a significant anxiolytic effect (Stough et al 2001). Another study of the same design tested brahmi in 76 adults over 3 months (Roodenrys et al 2002); significant improvements in a test for new information retention was observed, but there were no changes in the rate of learning.

In 2008, Calabrese et al demonstrated that whole plant standardised dry extract of *Bacopa monniera* (300 mg/day) safely enhanced cognitive performance in the aged in a double-blind, randomised, placebo-controlled study (Calabrese et al 2008). The trial involved 54 volunteers aged 65 years or older, without clinical signs of dementia, who received placebo or herbal treatment for 12 weeks. The group receiving active herbal treatment also experienced a reduction in anxiety whereas anxiety increased in the placebo group.

Results from other double-blind studies producing negative results indicate that cognitive effects require long-term use and are less likely to be seen in short-term or single-dose studies (Nathan et al 2001, 2004).

Anxiety

Bacopa has traditionally been used in Ayurvedic medicine to treat anxiety, and preliminary evidence is promising.

A placebo-controlled, randomised study of healthy subjects found that 300 mg of brahmi daily reduced the anxiety compared with placebo, an effect most pronounced after 12 weeks compared to 5 weeks of treatment (Stough et al 2001). Further randomised studies are warranted.

OTHER USES

In India, brahmi is traditionally recognised as a supportive treatment for mental illness and epilepsy. After clinical trials in human volunteers, a chemically standardised extract of BM has now been made available for prescription by the Central Drug Research Institute in India (Dhawan & Singh 1996). It has been shown to inhibit acetylcholinesterase (AChE) (Das et al 2002, Mukherjee et al 2007), so may have application in Alzheimer's dementia; however, clinical studies are unavailable to determine its efficacy.

Traditional uses

Bacopa has been traditionally used as a brain tonic and is commonly recommended to improve memory and heighten learning capacity. It is also used as a nerve tonic to treat anxiety, nervous exhaustion or debility and is prescribed to enhance rehabilitation after any injury causing nervous deficit, such as stroke. Other traditional uses include promoting longevity, and treating diarrhoea and asthma. It is used as an anti-inflammatory, analgesic, anxiolytic and antiepileptic agent with some support for these uses provided by in vitro and in vivo studies.

Irritable bowel syndrome

An Ayurvedic herbal combination consisting of *Aegle marmelos correa* and *Bacopa monniera* successfully treated 65% of patients with irritable bowel syndrome (IBS) under double-blind, randomised conditions (Yadav et al 1989). Herbal treatment was particularly useful in the diarrhoea-predominant form of IBS, compared with the placebo. Follow-up reviews 6 months after the trial found that relapse rates were the same among all test subjects. Although encouraging, it is not certain to what extent brahmi was responsible for these results.

DOSAGE RANGE

- Dried aerial parts of herb: 5–10 g/day.
- Fluid extract (1:2) or equivalent oral dose form: 5–13 mL/day in divided doses.
- Standardised extract 300–450 mg/day (Pravina et al 2007).

For children aged 6 years and older: 350 mg of dried plant extract in a syrup form was administered three times daily.

Standardised extract

BacoMind™ is an enriched phytochemical composition of *B. monniera*, and is standardised to the content of the following bioactive constituents:

- bacoside A_3 (> 5.0% w/w)
- bacopaside I (> 7.0% w/w)
- bacopaside II (> 5.5% w/w)
- jujubogenin isomer of bacopasaponin C (> 7.0% w/w)
- bacopasaponin C (> 4.5% w/w)
- bacosine (> 1.5% w/w)
- luteolin (> 0.2% w/w)
- apigenin (> 0.1% w/w)
- β-sitosterol-d-glucoside (> 0.3% w/w).

According to clinical studies

- Cognitive activator effects: 300 mg/day.

Positive results obtained in one controlled study have found that 5–12 weeks use is required before clinical effects are observed (Stough et al 2001).

TOXICITY

The LD_{50} data for an ethanolic extract of bacopa is 17 g/kg (oral) (Mills & Bone 2005).

Animal studies indicate that LD_{50} of standardised extract (BacoMind™) is 2400 mg/kg b.w. with no observed adverse effect limit (NOAEL) of 500 mg/kg b.w. after 90 days (Allan et al 2007).

ADVERSE REACTIONS

These may include minor gastrointestinal disturbances, nausea, palpitations, dry mouth, thirst and fatigue.

SIGNIFICANT INTERACTIONS

Controlled studies are not available, so interactions are based on evidence of activity and are largely theoretical and speculative.

Cholinergic drugs

Cholinergic activity has been identified for brahmi, therefore increased drug activity is theoretically possible — observe patient, although a beneficial interaction is possible under professional supervision.

CONTRAINDICATIONS AND PRECAUTIONS

Caution is advised in hyperthyroidism, as bacopa has been shown to significantly elevate T_4 levels in vivo. The clinical significance of this finding is unknown.

Brahmi may cause gastrointestinal symptoms in people with coeliac disease, fat malabsorption syndromes, vitamins A, D, E or K deficiency, dyspepsia or preexisting cholestasis due to the high saponins content of the herb (Mills & Bone 2005).

PRACTICE POINTS/PATIENT COUNSELLING

- Brahmi is an Ayurvedic herb that has been used for several thousand years as a brain tonic, to enhance intellect, treat psychiatric illness, epilepsy, insomnia and as a mild sedative.
- Evidence of cognitive activator activity from animal models of learning is positive.
  - Human studies have shown that brahmi has a significant effect on memory when used long-term; however, short-term use or single doses are unlikely to have an effect.
- Brahmi has potent antioxidant activity, which appears to be a result of both direct free radical scavenging activity and increasing endogenous antioxidant systems in the brain and liver.
- Anticholinesterase, antidepressant, antiulcer, antispasmodic, anti-inflammatory, antihistamine, neuroprotective and antinociceptive activities have been demonstrated in animal studies. Elevated T_4 levels have also been observed.
- Overall, large controlled studies are not available to determine the clinical significance of these effects, but existing evidence is promising.

PREGNANCY USE

Brahmi is recommended as a tonic for anxiety in pregnancy according to traditional Ayurvedic medicine; however, insufficient information is available to confirm safety during pregnancy.

PATIENTS' FAQs

What will this herb do for me?

Brahmi has a long history of use as a brain tonic. Results from scientific studies suggest that it may enhance memory and cognitive function and reduce anxiety with long-term use.

When will it start to work?

Studies suggest that 12 weeks' continual use is required for benefits on cognitive function to become apparent.

Are there any safety issues?

Information from traditional sources suggests that brahmi is well tolerated at the usual therapeutic doses, but scientific investigation has yet to establish whether drug interactions exist.

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Calcium

BACKGROUND AND RELEVANT PHARMACOKINETICS

In the context of both biosphere and biology (plant and animal) calcium plays a leading role. Its abundance in the environment (e.g. limestone, marble, coral) is reflected, in part, by its abundance in the human body; however, calcium homeostasis reflects a balancing act between requirements for proper function and the organism's need to protect against excess cellular calcium levels and associated toxicity. This balance has ramifications not only for our own physiology but also in terms of levels and bioavailability of dietary calcium.

Calcium, found in the diet or supplements, exists in salt form, from which it must be released for absorption to occur. Adequate hydrochloric acid levels are required to solubilise the majority of these calcium ions, failing which, calcium salts entering the higher pH environment of the small intestine are more likely to precipitate and be rendered insoluble (Wahlqvist 2002). Low or moderate calcium intakes (≤ 400 mg/d) are absorbed via active transport mechanisms that are influenced by vitamin D. When intake is high, active transport mechanisms become saturated, leading to greater passive absorption. Although most absorption occurs in the small intestine, the large intestine may also be responsible for up to 4% of absorption and provides compensatory mechanisms for those individuals with compromised small intestine absorption (Groff & Gropper 2009).

Calcium's bioavailability from both food and supplements shows enormous variation, from 4% to 45% (Recker 1985) and is dramatically influenced by other foods present in the gastrointestinal tract. Phytates, oxalates, all types of fibres, unabsorbed dietary fatty acids and other divalent minerals all potentially compromise its absorption, while lactose (especially in children) and other sugars, as well as protein and the presence of vitamin D all enhance uptake (Groff & Gropper 2009). There is also evidence of up to 60% inter-individual variance in calcium uptake; the underlying mechanisms, although unclear, may be linked to vitamin D receptor (VDR) polymorphisms (Heaney & Weaver 2003). Consistent with this, our understanding of the magnitude of vitamin D's influence upon calcium absorption continues to broaden, including the life-stage-dependent bioavailability of this mineral. The age-associated decline in calcium absorption (children absorb ≈ 75% compared with ≤ 30% in adults) (Groff & Gropper 2009) has now been linked to vitamin D via reduced available calcitriol and decreased intestinal VDR levels, producing vitamin D resistance (Groff & Gropper 2009, Pattanaungkul et al 2000). Similarly, the decreasing bioavailability associated with (peri)menopause and the increased absorption evident early in pregnancy (Prentice 2003) are attributed largely to vitamin D-mediated effects. Calcium absorption, however, is described as being generally inefficient, with a substantial amount of calcium remaining unabsorbed in the lumen (Heaney & Weaver 2003).

Distribution results in 99% of absorbed calcium being deposited in bones. The remainder of the absorbed calcium is present in teeth and the intracellular or extracellular fluids. Calcium is excreted in faeces, sweat and urine. Calcium homeostasis is tightly regulated by the actions of parathyroid hormone (PTH), calcitonin and vitamin D. Together, these hormones determine the level of absorption, excretion or retention by the kidneys, and sequestering or mobilisation of stores through bone mineralisation and resorption.

FOOD SOURCES

Good dietary sources of calcium include dairy products, fortified soy products, fish with bones, especially salmon and sardines, tofu, broccoli, collard greens, mustard greens, bok choy, clams and black strap molasses.

DEFICIENCY SIGNS AND SYMPTOMS

While there is little information available about the prevalence of deficiency across the general Australian population, a Melbourne study of 1045 women aged 20–92 years in 2000 revealed that approximately 76% of women consumed calcium at levels less than the recommended daily intake (RDI) and an additional 14% demonstrated a grossly inadequate intake of less than 300 mg/day (Pasco et al 2000). These figures are similar to those obtained by larger studies in the United States (Groff & Gropper 2009). Calculating the prevalence of calcium deficiency is partly hampered by physiological preservation of 'non-osseous' calcium for critical roles in exchange for the 'expendable' reserves in bone and, therefore, the slow development of overt deficiency features. Consequently, calcium deficiency is insidious in its early stages and potentially irreversible in the latter, making preventative optimisation the only successful pathway in all patients perceived to be at an increased risk. In addition to this, long-term suboptimal calcium has been linked to an increased risk of a range of other morbidities, including preeclampsia and colorectal cancer.

Deficiency signs and symptoms include:

- tetany: muscle pain, spasms and paraesthesias
- rickets
- osteomalacia
- increased neuromuscular irritability
- altered heart rate
- ambulatory developmental delays in children
- osteoporosis and increased risk of fractures
- bone pain and deformity
- tooth discolouration and increased decay
- hypertension
- increased risk of preeclampsia
- increased risk of colon cancer (controversial).

There are many situations and conditions in which the risk of hypocalcaemia may be increased.

Primary deficiency

Primary deficiency occurs as a result of inadequate dietary intake, with greatest risk seen in populations with increased calcium requirements e.g. children, adolescents, pregnant and lactating women, postmenopausal women, particularly those taking hormone replacement therapy (HRT) (Wahlqvist 2002), people experiencing rapid weight loss or patients receiving total parenteral nutrition (TPN).

Secondary deficiency

Calcium absorption is impaired in achlorhydria (more common in the elderly), intestinal inflammation and any malabsorptive disorder accompanied by steatorrhoea (Wilson et al 1991). Increased faecal calcium loss occurs with higher intakes of fibre and in fat malabsorption, while renal excretion has been shown in

some studies to be increased in those patients ingesting a high protein diet (Kerstetter et al 1998).

Factors that compromise vitamin D status or activity will also affect calcium status (Pattanaungkul et al 2000, Prince et al 1997) e.g. oral and inhaled corticosteroids (Beers & Berkow 2003, Rossi et al 2005).

Other conditions that can predispose to hypocalcaemia include hypoparathyroidism (a deficiency or absence of PTH), idiopathic hypoparathyroidism (an uncommon condition in which the parathyroid glands are absent or atrophied), pseudohypoparathyroidism (characterised not by deficiency of PTH, but by target organ resistance to its action), magnesium depletion, renal tubular disease, renal failure, acute pancreatitis, hypoproteinaemia, septic shock or the use of certain medicines such as anticonvulsants (phenytoin, phenobarbitone) and rifampicin, and corticosteroids (Beers & Berkow 2003, Rossi et al 2005).

MAIN ACTIONS

Calcium is an essential mineral required for the proper functioning of numerous intracellular and extracellular processes, including muscle contraction, nerve conduction, beating of the heart, hormone release, blood coagulation, energy production and maintenance of immune function. It also plays a role in intracellular signalling and is involved in the regulation of many enzymes.

Bone and teeth mineralisation

Calcium is found in bone where it is mainly complexed with other ions in the form of hydroxyapatite crystals. Approximately 1% of calcium in bone can be freely exchanged into the extracellular fluid in order to buffer changes in calcium balance.

Muscle contraction

Ionised serum calcium helps to initiate both smooth and skeletal muscle contraction and in particular, the regulation of rhythmic contraction of the heart muscle in combination with sodium and potassium.

Blood clotting

Calcium is involved in several steps of the blood clotting cascade.

Altered membrane functions

Calcium fluxes across membranes, both within the cell and across the plasma membrane, and acts as a vehicle for the signal transduction necessary for neurotransmitter and hormone function. It also selectively alters cell wall permeability to regulate passage of fluids in and out of cells.

OTHER ACTIONS

Regulates various enzyme systems responsible for muscle contraction, fat digestion and protein metabolism.

CLINICAL USE

Many of the indications for calcium supplements are conditions thought to arise from a gross or marginal deficiency; however, some are based on the concept of 'beyond-repletion' calcium therapy.

Calcium deficiency

Traditionally, calcium supplementation has been used to treat deficiency or prevent deficiency in high-risk conditions or people with increased calcium requirements such as pregnant women. Acute severe hypocalcaemic states are treated initially with intravenous infusion of calcium salts. In chronic cases, oral calcium supplements and occasionally vitamin D supplements are used.

Rickets and osteomalacia

A deficiency of either calcium or vitamin D can produce these bone disorders. (See Vitamin D monograph for further information.)

Infants

The percentage and type of fats within an infant formula and their ability to bind calcium salts and increase excretion has been shown to influence the bone mineral content (BMC) of infants. One hundred 8-week-old infants given formulas considered to be more similar to breastmilk and less likely to form calcium soaps in the gut showed increased BMC after only 1 month's treatment compared with those infants on standard formula (Kennedy et al 1999).

Bone mineral density (BMD) and osteoporosis prophylaxis

Children and adolescents

A 2006 Cochrane review of 19 trials, including 2859 participants, found no effect of calcium supplementation on femoral neck or lumbar spine BMD (Winzenberg et al 2006). There was a small effect on total body BMC and upper limb BMD; however, only the effect in the upper limb persisted after supplementation ceased. The effect is approximately equivalent to a 1.7% greater increase in supplemented groups, which, at best, would reduce absolute fracture risk in children by 0.1–0.2% annually. Additionally, there was no evidence of effect modification by baseline calcium intake, sex, ethnicity, physical activity or pubertal stage. The findings of this review, however, are contradicted by a more recent meta-analysis of 21 RCTs (Huncharek et al 2008b), which, while confirming a lack of effect in individuals with (near)adequate calcium intake at baseline, demonstrated significantly increased BMC (35–49 g) in those with a preexisting deficiency with long-term treatment. Overt critics of the methodology applied in the Cochrane review, another group of researchers undertook an 18-month study of calcium-deficient adolescent girls (average age 12 years), increasing their mean daily intake by 555 mg in the treatment group, yielding significantly increased BMC and BMD and reduced bone turnover markers in the treatment group compared with a placebo (Lambert et al 2008).

Adolescents

Peak bone mass is one of the main determinants of osteoporotic fracture in humans and, therefore, there is significant research dedicated to determine the influence of calcium status on the 40–50% peak

bone mass accretion that occurs during adolescence. Overall, studies in adolescent girls have shown that calcium supplementation significantly improves bone mineral status. Numerous studies, including one by Stear et al in 2003 of 144 pubertal girls, have confirmed a synergistic relationship between mechanical load, through physical activity, calcium status and bone calcium accumulation; however, it is important to note that physical activity has a positive effect on BMD only at high calcium intakes, with no effect at calcium intakes of less than 1000 mg/day (Harkness & Bonny 2005).

Until recently, all clinical trials with calcium supplements in children and adolescents demonstrating a positive effect on bone mass were conducted over durations of 1–3 years. As such, it is uncertain whether supplementation and resultant increases in bone mass had a beneficial effect in the long-term. A 2005 placebo-controlled study addressed this issue by using calcium supplements (670 mg/d) over a 7-year period. The study of 354 pubertal girls reported significant increases in BMD during growth spurts in the supplemented group; however, these gains did not uniformly persist into late adolescence and only girls of tall stature received long-lasting benefits. Interestingly, the placebo group exhibited a 'catch-up' in bone mineral accretion subsequent to the pubertal growth spurt (Matkovic et al 2005). These results introduce two novel concepts: the first being that dietary calcium requirement for skeletal development may be size dependent and, secondly, the possibility that a calcium mineral deficit may be a transient feature of the pubertal growth spurt, with a 'catch-up' possible during bone consolidation. In spite of these findings, the temporary gains in BMD may be important in the prevention of fractures during adolescence (Matkovic et al 2005).

A second study introduces other issues regarding the impact of variable calcium status in adolescents. The RCT of 144 prepubertal girls used 850 mg/d of calcium over 1 year. After follow-up some 7 years later, in addition to positive effects on BMD outcomes, an inverse relationship became apparent between calcium supplementation and age of menarche. The authors speculate that higher calcium intake prior to menarche may favourably impact on long-term BMD through this dual mechanism (Chevalley et al 2005).

Postmenopausal women

Numerous studies have confirmed an important role for calcium in the prevention of osteoporosis in postmenopausal women. Clinical studies have assessed its efficacy as a sole agent against placebo, in comparison with steroid hormones, antiresorptive drugs and as part of combination therapy.

Long-term supplementation with calcium protects against bone loss according to a 2-year study involving 60 postmenopausal, non-osteoporotic women. The trial showed that in comparison with the 3% BMD loss evident in the placebo group, those consuming 1633 mg/day on average of supplemental calcium suffered no bone loss, as measured at the greater trochanter, and, in fact, their BMD improved at other sites tested (Storm et al 1998). A similar trend was demonstrated by Daniele et al (2004) in their study of 120 women, given only 500 mg of calcium and 200 IU of vitamin D per day over 30 months. In general, though, the efficacy of calcium supplements in postmenopausal women appears to be largely dependent upon the baseline calcium intake. Those with an initial poor intake tend to achieve significant improvements over placebo, with more modest or no effect evident in groups with higher intakes at baseline (Daniele et al 2004, Fardellone et al 1998).

Whether calcium supplements are sufficient as a stand-alone preventative measure against osteoporosis is still being investigated. The results of one study suggest that the effects of calcium on BMD may require additional supplementation with the trace minerals zinc, manganese and copper (Strause et al 1994). However, the most impressive results obtained to date are for the combination of high-dose calcium with antiresorptive drugs such as oestrogen or calcitonin. A review of these studies highlights the gain in bone mass that resulted from the addition of calcium in contrast to the halt in BMD depletion commonly observed with use of calcitonin alone (Nieves et al 1998).

Other studies of both male (n = 50) and female (n = 200) populations using a combination of fluoride, as monofluorophosphate, and calcium over a 3–4-year period, found this combination to be superior to calcium alone in the prevention of BMD loss. Increased lumbar spine BMD and reduced risk of fractures was evident in both trials using the two minerals (Reginster et al 1998, Ringe et al 1998).

Men

The overwhelming majority of calcium studies for bone health have been conducted in postmenopausal women and often their results have simply been extrapolated to produce clinical protocols for men regarding osteoporosis prevention and management. The few studies conducted in male populations, while not always unanimous, have shown no benefit at 600 mg/day, while yielding BMD improvements secondary to higher doses (1200 mg/day) comparable with postmenopausal women. Enhanced results in some studies may be attributable to the addition of vitamin D (Reid et al 2008).

The elderly

A number of large studies investigating the preventative effect of calcium alone or in combination with vitamin D have produced predominantly positive results in the elderly. Studies by Chapuy et al (1992, 1994, 2002), Dawson-Hughes et al (1997) and Larsen et al (2004) demonstrate a significant reduction in fracture risk (≤ 16%), while a recent meta-analysis of 29 RCTs conducted in 63,897 individuals of 50 years and above, over an average of 3.5 years, also concluded that calcium alone (≥ 1200 mg/day) or in combination with vitamin D (≥ 800 IU/day) reduced the risk of fracture by 12–24% and reduced bone loss by 0.54% at the hip and 1.19% at the spine (Tang et al 2007).

Greatest improvements were noted specifically in the elderly, institutionalised, underweight and calcium deficient. Adding to this, a recent Australian trial investigating 1200 mg/day of calcium administered alone or combination with 1000 IU vitamin D over 5 years in 120 women aged 70–80 years yielded beneficial effects on BMD and bone turnover markers for both treatment groups, with evidence of more sustained improvements in those also taking vitamin D (Zhu et al 2008). The RECORD Trial in 2005, a RCT of 5292 people aged 70 years or older who received either 1000 mg of calcium or 800 IU of vitamin D/day, alone or together, for 24–62 months, however, failed to yield positive findings (The RECORD Trial group 2005). The authors postulate that improved results in previous studies may be due to the increased age (> 80 years) of study volunteers and poorer vitamin D status at baseline; however, the results of the studies cited here contradict this supposition.

Glucocorticoid-induced osteoporosis

Approximately one in six people with asthma receiving inhaled and/or systemic glucocorticoids developed fractures over 5 years. The interaction with calcium plays a small role in this process, with glucocorticoids directly inhibiting vitamin D-mediated intestinal absorption of calcium. High vitamin D doses (50,000 IU twice weekly) in combination with 1.5 g calcium daily can overcome this interference (Wilson et al 1991), whereas a randomised study found that treatment with calcium alone or in combination with etidronate may not be effective. A study of 352 volunteers found that treatment for 5 years did not significantly reduce the fracture rate (Campbell et al 2004).

Supplementation during pregnancy and lactation

Evidence from 1997 found that approximately 40% of primiparous Australian women failed to meet the RDI for calcium. Considered a critical nutrient during pregnancy with at least a twofold increase in requirements observed, its metabolism during gestation significantly changes from as early as 12 weeks, with doubling of both absorption and excretion, followed by additional losses through lactation, which can account for reductions in maternal bone mineral content of 3–10% (Prentice 2003). While it is clear that general supplementation would be necessary in those women with poor preconception calcium levels, it is suggested that for healthy women the metabolic compensation evident in pregnancy should be sufficient to guarantee adequate fetal levels.

Prevention of hypertension and preeclampsia

Epidemiological evidence illustrates an inverse relationship between calcium status and the prevalence of preeclampsia (Frederick et al 2005, Lopez-Jaramillo et al 2001) and recent studies confirm abnormalities in markers of calcium metabolism and status in preeclamptic populations compared to controls, including low urinary and serum calcium levels (Ingec et al 2006, Sukonpan & Phupong 2005). Trials that included a 1996 meta-analysis of studies involving calcium and hypertension in pregnancy have shown a substantial mean reduction in both systolic blood pressure (SBP) and diastolic blood pressure (DBP), which was also confirmed by more recent reviews (Atallah et al 2002, Bucher et al 1996).

Positive correlations demonstrated in original smaller trials between calcium supplementation and reduced prevalence of preeclampsia, involving over 400 women, were put into question when the Calcium for Prevention of Pre-eclampsia study (CPEP), the largest trial to date, found no effect on the incidence or severity of the condition (Levine et al 1997). However, the CPEP study, involving over 4000 healthy nulliparous women, was not a replication of the existing trials. While the original studies used populations with a low calcium intake to ascertain the connection between correction of this deficiency and prevalence of preeclampsia, the CPEP represented a 'pharmacological intervention in women with a normal calcium intake' (Lopez-Jaramillo et al 2001). A large study conducted by the WHO in eight countries of 8325 low-calcium-consuming women (< 600 mg/day), also failed to demonstrate a preventative effect for high-dose calcium; however, supplementation did reduce the severity of preeclampsia, in addition to reducing maternal morbidity and maternal (RR 0.80) and neonatal mortality (RR 0.70) (Villar et al 2006).

Further reviews of studies involving over 15,000 women, however, have supported calcium's preventative role with researchers demonstrating significant risk reduction in both low-risk (RR 0.48) and high-risk women (RR 0.22), hence, concluding calcium supplementation should be recommended for those women with a low calcium intake who are at risk of developing gestational hypertension (Crowther et al 1999, Hofmeyr et al 2003, 2006, 2007).

There is currently no unanimous explanation for calcium's protective effect (Villar et al 2003). While the antagonistic relationship between calcium and lead has been previously hypothesised to be involved (Sowers et al 2002), recent evidence of calcium's lack of effect on platelet count, plasma urate and proteinuria, in spite of reducing pre-eclamptic incidence, implies that high-dose calcium effectively lowers blood pressure without influencing the condition's underlying pathology (Hofmeyr et al 2008).

A small number of studies have investigated the effects of calcium in combination with other nutrients, including antioxidant and omega-3 oils in this population. One randomised, placebo-controlled, double-blind study involving a sample of 48 primigravidas, using a combination of 600 mg/day calcium and 450 mg/day of conjugated linoleic acid (CLA) from weeks 18–22 until delivery, resulted in a significantly reduced incidence of pregnancy-induced hypertension (8% vs 42% of the control group) (Herrera et al 2005). Further studies are warranted to elicit the individual impact of both nutrients and to determine the superiority of sole or combination treatment.

Leg cramps

Calcium supplements are commonly prescribed in pregnancy when leg cramps are a problem. A Cochrane review of five trials involving 352 women taking various supplements for the treatment of leg cramps in pregnancy included only one placebo-controlled trial of calcium. From this, researchers concluded that any improvement in cramps in those groups treated solely with calcium was likely due to a placebo effect, with significant findings limited to the groups taking other nutrients (Young & Jewell 2002).

Fetal growth

The greatest period of fetal mineral accretion has been identified as the gestational period of 20–33 weeks, with daily needs escalating from 50 mg/day to 330 mg/day at its peak. The average newborn contains about 20–30 g calcium, and one study of 256 women in their second trimester showed that supplementation in women with poor calcium status significantly increased neonatal bone mineral content, as determined by X-ray absorptiometry measurements at 1-week post-partum (Koo et al 1999). However, the full relationship between maternal calcium intake and fetal growth, particularly in non-deficient women, has yet to be elucidated (Prentice 2003). One suggested effect of gestational mineral intake has been the determination of calcium concentration in the mother's breast milk, while it has been established that this concentration is not the result of calcium intake postpartum (Prentice et al 1999).

Lead toxicity

Increased blood lead levels are commonly a result of bone resorption during pregnancy and are considered a potential risk to fetal and infant health. Lead can be transferred to the fetus and infant via cord blood and breastmilk. Several studies suggest a low placental barrier to lead, with 79% of the mobilised lead from maternal bone passed to the infant (Dorea & Donangelo 2005). While a number of studies have indicated lead levels in the breastmilk of Australian women appear to be well within a safe range, recent data from a study conducted by Ettinger et al revealed that even low lead content in human milk appears to be highly influential on the lead levels of infants in their first month of life (Ettinger et al 2004). A separate review published in 2005 discussed additional related trends such as increased lead concentrations in cord blood during winter months, because of lower vitamin D status (Dorea 2004).

A RCT of 617 lactating women supplemented with high-dose calcium carbonate found that the women in the calcium group showed significant reductions in blood lead levels. Those subjects who showed improved compliance and also had baseline higher bone lead content produced an overall reduction of 16.4% (Hernandez-Avila et al 2003). Similar positive findings came from a study in Mexico of 367 lactating women; however, the maximal reduction in lead concentrations reached only 10% (Ettinger et al 2006). Nevertheless, when considered together these results suggest that calcium supplementation may represent an important interventional strategy, albeit with a modest effect, for reducing infant lead exposure.

Neonatal benefits

Calcium supplementation during pregnancy has been postulated to have prolonged benefits in the offspring, as indicated in a study of nearly 600 children aged 5–9 years whose mothers had previously participated in a calcium trial during their pregnancy. The children demonstrated reduced SBP, compared with the children whose mothers had taken placebo, with significance reached particularly for those in the upper BMI bracket (Belizan et al 1997). More recent reviews, while still demonstrating some association between gestational calcium supplementation and reduced blood pressure and incidence of hypertension in the offspring (particularly older children e.g. 7 years), highlight the weakness of the evidence to date, including small sample sizes, methodological issues and the fact that most of the studies have been conducted in developed countries where calcium intake is more likely to be adequate (Bergel & Barros 2007, Hiller et al 2007).

Dyspepsia

A first-line over-the-counter (OTC) treatment for heartburn, indigestion and dyspepsia has often been an antacid, based on calcium carbonate in combination with magnesium and aluminium salts. Calcium in combination with the other ingredients reduces stomach acid and increases the rate of gastric emptying (Vatier et al 1996). In trials comparing H_2 blockers with calcium carbonate tablets, calcium was found to be equipotent, yet delivered a more rapid response and shorter duration of action (Feldman 1996). There have been many papers highlighting the dangers of prolonged use of these traditional antacids; however, pure calcium carbonate formulas attract the least concern, with the incidence of 'milk alkali syndrome' resulting from their overuse reported to be rare (Ching & Lam 1994, Herzog & Holtermuller 1982).

Prevention of cancer

Interest in a relationship between dairy consumption and cancer incidence continues to grow, with evidence of both protective and contributory effects dependent upon both cancer type and timing of exposure. The consumption of dairy products, however, represents a mix of numerous variables and biological pathways that potentially convey these underlying actions, from which calcium's role is difficult to extricate (van der Pols et al 2007). An interventional study of calcium (1400–1500 mg/day), alone or with vitamin D_3 (1100 IU/day), compared to placebo over 4 years, offers more specific information regarding calcium's role in cancer (Lappe et al 2007). The study, conducted in 1179 women of more than 55 years, was primarily designed to assess effects on fracture incidence; however, upon further analysis also demonstrated significant risk reduction (RR 0.40) for all cancer incidence

amongst the calcium and vitamin D group. When the analysis was restricted to only those cancers diagnosed after the first year of treatment, the RR became 0.23. While the group receiving calcium alone also demonstrated a reduced risk, the researchers speculate that this may not be robust and conclude that vitamin D is the key variable in reduced incidence of all cancer.

Prevention of colorectal cancer and recurrence of adenomatous polyps

Currently, the gold standard for measuring risk reduction by an intervention in colorectal cancer investigates the incidence of recurrence of adenomatous polyps following removal of all colonic polyps by polypectomy; further analyses evaluate reduction of total adenomatous polyps and reduction of advanced polyps as defined by size and the presence of severe dysplasia. Reasonably consistent evidence suggests that calcium supplementation of 1200 mg/d reduces total adenomas by approximately 20% and advanced adenomas by about 45% (Holt 2008). Interestingly, some studies show that calcium's protective effect against recurrent adenomas is largely restricted to individuals with baseline serum 25-hydroxy vitamin D above the median (≈ 29 ng/mL). These data, together with more recent findings (Mizoue et al 2008), strongly point to the importance of both calcium and vitamin D for reducing colorectal cancer risk and altering adenoma recurrence (Grau et al 2003, Holt 2008, Oh et al 2007).

Interactions between calcium and other variables in colorectal carcinogenesis have also been explored, revealing gender-specific results; protective in males but not in females in most (Ishihara et al 2008, Jacobs et al 2007, Ryan-Harshman & Aldoori 2007), but not all, studies. Further research, including re-analysis of the Women's Health Initiative (WHI) findings pertaining to colorectal cancer incidence, has elucidated oestrogen's critical modifying effect upon calcium, whereby the higher oestrogen levels of both menstruating and postmenopausal women taking HRT negate calcium's otherwise protective effect (Ding et al 2008). Explanations for this phenomenon include oestrogen's influence upon calcium distribution: removing it from circulation for bone deposition and competition for binding evident between vitamin D and oestrogen (Ding et al 2008, Oh et al 2007).

Early hypotheses regarding calcium's general protective effects focused on its ability to bind bowel-irritating substances secreted into bile. This notion is further supported by a number of studies demonstrating enhanced chemoprotection when high doses of calcium have been combined with dietary factors such as reduced fat and increased carbohydrate, fibre and fluid intakes (Hyman et al 1998, Rozen et al 2001, Schatzkin & Peters 2004).

One significant development in our understanding has been the discovery of human parathyroid calcium-sensing receptors in the human colon epithelium, which function to regulate epithelial proliferation and differentiation. New in vitro studies suggest that expression of these receptors may be induced by the presence of extracellular calcium and vitamin D, therefore promoting greater differentiation of the epithelial cells (Chakrabarty et al 2005, Holt 2008) and inducing apoptosis (Miller et al 2005).

A 2005 Cochrane review examining the effect of supplementary calcium on the incidence of colorectal cancer and the incidence or recurrence of adenomatous polyps included two double-blind, placebo-controlled trials with a pooled population of 1346 subjects. Doses of supplementary elemental calcium used were 1200–2000 mg/day for 3–4 years. Reviewers concluded that, while the evidence to date appears promising and suggests a moderate degree of prevention against colorectal adenomatous polyps, more research with similar findings is required before this can be translated into any preventative protocol (Weingarten et al 2005).

Clear parameters for dosing are not yet available, with some studies showing no further benefit above 700–800 mg/day of total calcium, while other studies suggest an ongoing inverse dose-dependent relationship without cutoff (Schatzkin & Peters 2004). Current evidence for a combined protective role of calcium, either dietary or supplemental, and vitamin D, particularly in men and postmenopausal women not taking HRT, is strong and further elucidation of the independent and combined effects of these nutrients will assist in the development of preventative protocols.

Other cancers

Ongoing research regarding calcium's potential role in a range of other cancers suggests a possible protective effect against breast and ovarian cancers (Genkinger et al 2006, McCullough et al 2005, 2008); however, the research remains preliminary and largely of epidemiological design. A greater body of evidence has developed regarding the interplay between calcium and prostate cancer, with initial findings touting a positive association between dairy product consumption, total dietary calcium intake (especially >1500 mg/day) and risk. The results of ongoing extensive, prospective epidemiological research involving hundreds of thousands of men, however, have been conflicting, both confirming (Ahn et al 2008, Gao et al 2005) and negating (Huncharek et al 2008a, Park et al 2007a & b) earlier evidence. Two important details have recently emerged regarding the potential interaction between calcium and prostate cancer risk with several studies consistently demonstrating that calcium derived from supplements does not convey a greater risk (Ahn et al 2008, Baron et al 2005, Park et al 2007a) and limiting calcium as a risk factor only when consumed as dairy products, while greater non-dairy calcium intake appears to lower the risk (Allen et al 2008, Park et al 2007b). A prospective study of serum calcium adds to the riddle, revealing that results in the highest tertile typically more than 9 years prior to diagnosis were strongly associated with increased risk of fatal prostate cancer (Skinner & Schwartz 2008); however, such results may be indicative of calcium dysregulation rather than high intakes.

Hypertension

Ongoing broad-scale international epidemiological data, including prospective studies, link low dietary calcium intake, with a slightly increased risk of hypertension (Alonso et al 2005, Elliott et al 2008, Geleijnse et al 2005, Wang et al 2008). Conversely, increased dietary calcium, typically in the form of low-fat dairy products, has been shown to be independently protective (RR 0.87 for highest quintile of calcium intake) (Alonso et al 2005, Wang et al 2008). A recent study found that high dietary calcium was associated with SBP/DBP reductions of −2.42/−1.48 mmHg, after controlling for other known risk factors (Elliott et al 2008). This effect was more pronounced when accompanied by increased magnesium and phosphorus consumption. Interestingly, neither high-fat dairy products nor calcium supplements convey protection (Wang et al 2008)

Additional findings attracting attention include epidemiologic links between markers of low calcium status or calcium metabolism abnormalities, hypertension and insulin resistance. Supporting the possible link between these phenomena are the results of a Japanese study of 34 non-diabetic hypertensive and 34 non-diabetic normotensive women. Multiple group assessments revealed statistically significant increased urinary calcium, lower BMD, depressed serum calcium and elevated circulating PTH in the hypertensive sample (Gotoh et al 2005).

Underlying mechanisms for calcium's protective effect are speculated to involve reduced calcium influx into cells, inhibiting vascular smooth muscle cell constriction, reduced activity of the renin–angiotensin system and improved Na/K balance (Wang et al 2008).

A 2006 Cochrane review of 13 RCTs involving 485 volunteers found that calcium supplementation significantly reduced SBP (mean difference: −2.5 mmHg), but not DBP (mean difference: −0.8 mmHg) compared with controls (Dickinson et al 2006). The authors temper their conclusion, stating that the quality of included trials was poor and the heterogeneity between trials means there is a tendency to overestimate treatment effects. Earlier, an extensive systematic review, updated in 1999 to include 42 randomised comparative trials, showed modest reductions in both SBP and DBP (−2 mmHg and −1 mmHg, respectively) with 1–2 g/day calcium over a 4–14-week intervention (Griffith et al 1999). Dietary calcium appeared to have a larger effect than supplementation, a finding reiterated in more recent studies (Wang et al 2008). The clinical significance of these small effects has been questioned and the recommendation of calcium as a therapy for all types of hypertension appears premature (Kawano et al 1998), particularly in light of more recent negative findings from the WHI, which investigated the effects of 1 g of calcium together with 400 IU of vitamin D over a median follow-up period of 7 years in postmenopausal women (Margolis et al 2008). Some studies have proposed that it is only a particular hypertensive subset that is calcium responsive. A number of researchers, for example, have hypothesised a physiological correlation between 'salt sensitive' hypertension and responsiveness to calcium treatment (Coruzzi & Mossini 1997, Resnick 1999). The link may be that sodium excess encourages calcium losses. This theory is further supported by a recent epidemiological study demonstrating that, while blood pressure was inversely correlated with dietary calcium, further analysis revealed sodium intake to be the primary influence, increasing pressures while concomitantly reducing BMD (Woo et al 2008).

Premenstrual syndrome

Of all the vitamins and minerals used in the treatment of premenstrual syndrome (PMS), calcium supplements show overwhelmingly positive results.

One of the earliest trials to show that calcium supplementation can alleviate symptoms in PMS was conducted in 1989 (Thys-Jacobs et al 1989). A randomised, double-blind, crossover trial involving 33 women with confirmed PMS compared the effects of daily 1000 mg calcium carbonate with placebo over 6 months. Results showed that 73% of women reported improved symptoms while taking calcium supplementation, whereas 15% preferred placebo. The premenstrual symptoms responding significantly to calcium supplementation were mood changes, water retention and premenstrual pain. Menstrual pain was also significantly alleviated.

In 1993, the *American Journal of Obstetrics and Gynecology* published a study that compared the effects of calcium (587 mg or 1336 mg) and manganese (1.0 mg or 5.6 mg) on menstrual symptoms. Ten women with normal menstrual cycles were observed over four 39-day periods during the trial (Penland & Johnson 1993). The researchers found that increasing calcium intake reduced mood, concentration and behavioural symptoms generally and reduced water retention during the premenstrual phase. Additionally, menstrual pain was reduced.

A more recent large, double-blind, placebo-controlled, randomised parallel-group study was conducted in the United States and supports the previous findings (Thys-Jacobs et al 1998). Four hundred and sixty-six premenopausal women with confirmed moderate to severe PMS were randomly assigned to receive either 1200 mg elemental calcium (from calcium carbonate) or placebo for three menstrual cycles. Symptoms were documented daily by the subjects based on 17 core symptoms and four symptom factors (negative affect, water retention, food cravings and pain). Additionally, adverse effects and compliance were monitored daily. During the luteal phases of both the second and third treatment cycles, a significantly lower mean symptom score was observed in the calcium group. By the third treatment cycle, calcium treatment resulted in a 48% reduction in total symptom score compared with baseline, whereas placebo achieved a 30% reduction. Furthermore, all four symptom factors responded in the calcium-treated group.

A 1999 review of multiple trials investigating calcium supplementation as an effective therapy for PMS has found overwhelming positive results (Ward & Holimon 1999).

Some researchers in this area have hypothesised that part of the PMS aetiology lies in calcium dysregulation in the luteal phase and have highlighted the dramatic similarities between symptoms of PMS and hypocalcaemia (Thys-Jacobs 2000). Recent data from the Nurses' Health Study II support this theory, with evidence of low calcium and vitamin D levels in PMS populations when compared to controls (Bertone-Johnson et al 2005).

Weight loss

Although the underlying mechanism of action remains unclear, there is general acceptance that high calcium intake, particularly in the form of dairy products, and more recently calcium-fortified soy (Lukaszuk et al 2007), depresses PTH levels and $1,25(OH)_2D$, which in turn decreases intracellular calcium, thereby potentially inhibiting lipogenesis and stimulating lipolysis (Major et al 2007, McCarty & Thomas 2003, Schrager 2005, Zemel et al 2004). Additional proposed actions include increased rates of faecal fat and energy excretion (14.2 g/day vs 5.9 g/day and 1045 kJ/day vs 684 kJ/day), as observed in a preliminary study of 10 subjects during a 1-week high-calcium and normal protein diet (1800 mg/day and 15% of total energy intake, respectively) (Jacobsen et al 2005). More recent evidence also points to a potential satiety effect (Kabrnova-Hlavata et al 2008).

A prolific researcher in this area is Zemel (2004, Zemel et al 2004, 2005a, 2005b), having published three small trials investigating the effects of dietary and supplemental calcium in patients for weight maintenance or weight loss. These trials have consistently yielded positive results, demonstrating that in addition to enhanced weight loss on isocaloric and identical macronutrient profiles, with or without energy restriction, a diet providing high calcium levels of 1100–1200 mg/day results in central fat loss and corresponding improvements in blood pressure, insulin sensitivity and retention of lean tissue. Australian researchers, Bowen et al, have also demonstrated similar results (Bowen et al 2004). Zemel et al conclude that dietary calcium and, in particular, dairy-based foods are the most effective form of calcium for weight loss and that results are significant within 12 weeks.

An early review by Teegarden (2003), bringing together trials dating back 10 years to the first rat studies and updated in 2005, while acknowledging the promising data in relation to increased consumption of dairy products and weight management which had emerged over the intervening 2 years, noted the limitations of the current body of evidence that required addressing to elucidate the full extent of calcium's effect on weight. A more recent meta-analysis of 13 RCTs investigating calcium interventions ranging between 610 mg and 2400 mg/day over a period of 12 weeks–36 months, failed to demonstrate a positive effect on weight loss for either calcium supplements or dairy products; however, once again methodological concerns were raised (Trowman et al 2006). In spite of this, studies have continued to emerge yielding positive findings in postmenopausal women as part of the WHI study (calcium and vitamin D treatment reducing risk of weight gain by 11%) (Caan et al 2007) and in overweight and obese type 2 diabetic patients (> 8% more weight loss in those consuming calcium in the highest compared with the lowest tertile) (Shahar et al 2007). Additionally, one small study demonstrated an augmenting effect of calcium (1200 mg together with 400 IU vitamin D/day) over 15 weeks on weight loss-induced beneficial changes to blood lipids and lipoproteins (Major et al 2007).

In contrast to this, there have been a number of studies reporting negative results. A trial of isocaloric energy-restricted diets in 54 overweight subjects with either low or high calcium intake from dairy products found that over 12 months there was no significant difference in weight loss between the two groups (Harvey-Berino et al 2005). Other studies incorporating calcium supplements of 1000 mg/day yielded negative results over three 25-week periods in pre- and postmenopausal women (Shapses et al 2004), as did a longitudinal study of dietary habits in adolescents (Berkey et al 2005), and calcium augmentation of a 3-week weight management program in overweight individuals; however, in the latter both the dose and the duration of the study appear inadequate (Kabrnova-Hlavata et al 2008).

Finally, caution is being encouraged by many authorities who are keen to remind researchers that epidemiological data have positively linked high dairy diets with a range of other conditions, most notably prostate cancer (Lanou 2005).

Nephrolithiasis

In spite of previous concerns regarding a causal relationship between dietary or supplemental calcium intake and the recurrence of oxalate stones, recent studies demonstrate that this fear appears unfounded. Collectively, the evidence points more towards a protective effect for increased dietary calcium, in relation to both urinary oxalate concentrations (Taylor & Curhan 2004) and reduced stone formation (Goldfarb 2009). The current view is that, rather than being a contributing factor for oxalate stones, dietary calcium, through its binding of oxalate in the gut, can minimise recurrence, as substantiated by other studies (Curhan et al 1997, Liebman & Chai 1997).

One study comprised 120 men with recurrent calcium oxalate stones due to idiopathic hypercalciuria and who were randomly assigned to either a low-calcium diet or low-animal protein, low-salt normal-calcium diet and assessed for changes in frequency of stone formation. Results clearly showed reduced oxalate excretion in those on a normal calcium intake, as well as a greater decrease in calcium oxalate saturation (Borghi et al 2002). In another study of 14 healthy men, assessment of the influence of dietary calcium on the given amount of oxalate demonstrated that with the inclusion of additional calcium (1121 mg) urinary oxalate levels increased in the control but not in the treatment group (Hess et al 1998).

OTHER USES

Hyperlipidaemia

In a randomised, placebo-controlled crossover trial of 56 patients with mild–moderate hypercholesterolaemia on a controlled low-cholesterol diet, calcium

Clinical note — Is calcium supplementation a risk for increased vascular events?

Recently, concern has emerged regarding a potential increase in cardiovascular events associated with long-term high-dose calcium supplementation. This is largely the result of a New Zealand RCT investigating the effect of calcium supplements (1000 mg/d) administered to 1471 healthy postmenopausal women over 5 years (Bolland et al 2008). The primary outcome of this study was bone density; however, the researchers also hypothesised that a secondary effect of the treatment would be a reduction in heart attacks, based on existing observational studies highlighting calcium's positive effect on blood lipids and blood pressure (Nainggolan 2008). However, much to the researchers' surprise, secondary analysis of the data revealed that women taking calcium supplements experienced higher rates of myocardial infarction (RR 1.49), all vascular events (RR 1.21) and stroke (RR 1.37), translating to 23.3/1000 persons annually versus 16.3/1000 persons annually for the women taking placebo. While the authors conclude that their study does not unequivocally demonstrate causality, they cite three other large studies with somewhat similar findings, including secondary analyses of the WHI which yielded a RR of 1.18 for older heavier women taking calcium and vitamin D. Speculation regarding a potential mechanism of action includes raised serum calcium which may accelerate vascular calcification, predictive of vascular events. The authors also flag the possibility that, similar to the WHI findings, a particular subset of individuals may be at an elevated risk due to increasing age (average age of study participants was 74 years), preexisting cardiovascular disease and declining renal function.

While such findings initially cause substantial alarm and warrant further thorough investigation, the fact that a comparable number of other large calcium studies, e.g. Iowa Women's Health Study, Boston Nurses' Health Study, have failed to demonstrate this relationship, or in fact have found a protective effect, must also be considered. In addition to this, it is interesting to reflect on the possible interplay between calcium, magnesium, oestrogen and cardiovascular risk, as have Seelig et al (2004). These researchers propose that an elevated ratio of Ca:Mg induces a procoagulatory environment, which would theoretically be compounded by exogenous oestrogen in the form of HRT. In accordance with this, they have hypothesised that the increased rates of cardiovascular events seen amongst the WHI participants is a consequence of these interactions and excessive calcium supplementation without magnesium is inherently dangerous in such a population.

carbonate supplementation was shown to significantly reduce LDL levels by 4.4%, with additional 4.1% increases in HDL levels. No other effects on other blood lipids or blood pressure were observed (Bell et al 1992). Another small study demonstrated an augmenting effect of calcium (1200 mg together with 400 IU vitamin D/day) over 15 weeks on weight loss-induced beneficial changes to blood lipids and lipoproteins, with significantly greater reductions in total:HDL, LDL:HDL and LDL levels (Major et al 2007).

Dry eye

A controlled double-masked study of petrolatum ointment containing 10% w/w calcium carbonate applied on the lower lid twice daily for 3 months resulted in significant improvements in all criteria assessed. However, significance over placebo was only found in ocular surface staining, therefore determination of the action of petrolatum needs to be established and controlled in future studies to identify the therapeutic value of calcium (Tsubota et al 1999).

Fluorosis

Calcium has been shown to reduce the clinical manifestations of fluorosis in children exposed to contaminated water (Gupta et al 1996).

DOSAGE RANGE

Australian RDIs

- Infants
  - 1–3 years: 500 mg/day.
  - 4–8 years: 700 mg/day.
- Children
  - 9–11 years: 1000 mg/day.
  - 12–18 years: 1300 mg/day.
- Adults
  - < 70 years: 1000 mg/day.
  - > 70 years: 1300 mg/day.
- Pregnancy: 1000–1300 mg/day.
- Lactation: 1000–1300 mg/day.

According to clinical studies

- Osteoporosis prophylaxis: 1500 mg/day in combination with accessory nutrients (e.g. zinc, manganese, copper and fluoride, HRT or antiresorptive drugs).
- Premenstrual syndrome: 1200–1600 mg/day.
- Prevention of preeclampsia: 2000 mg/day.
- Increased BMD in children with low intake: 100 mg/day.
- Supplementation during pregnancy to increase mineral accretion in fetus: 2000 mg/day for last trimester.
- Allergic rhinitis: 100 mg/day.
- Hyperacidity: 500–1500 mg/day as required.
- Hyperlipidaemia: 400 mg three times daily.
- Hypertension: 1000–2000 mg/day.
- Dry eye: 10% w/w calcium carbonate in petrolatum base applied twice daily.
- Fluorosis in children: 250 mg/day.
- Prevention of colorectal cancer: 1200 mg/day.
- Weight loss: 1000–1200 mg/day long term.

ADVERSE REACTIONS

Oral administration of calcium supplements may cause gastrointestinal irritation, constipation and flatulence.

Hypercalcaemia
Increased serum calcium may be associated with anorexia, nausea and vomiting, constipation, hypotonia, depression and occasionally lethargy and coma. Prolonged hypercalcaemic states, especially if associated with normal or elevated serum phosphate, can precipitate ectopic calcification of blood vessels, connective tissues around joints, gastric mucosa, cornea and renal tissue (Wilson et al 1991).

SIGNIFICANT INTERACTIONS
Calcium carbonate when taken as an antacid alters the absorption and excretion of a wide range of drugs. Please refer to a drug interaction guide for specific concerns. Only those interactions encountered with oral administration of calcium supplements will be included in this section.

Alendronate
Calcium causes decreased absorption of this drug. However, as calcium supplementation is a fundamental adjuvant to the prevention of BMD loss, supplementation should still be encouraged — separate doses by at least 2 hours.

Atenolol
Simultaneous use can reduce bioavailability of both agents — separate dose by 2 hours.

Caffeine
Caffeine increases urinary excretion of calcium — ensure adequate calcium intake and monitor for signs and symptoms of deficiency.

Calcium channel blockers
Calcium supplements can have an antagonistic effect on the desired action of calcium channel blockers that could precipitate the re-emergence of arrythmias — avoid high-dose supplements unless under professional supervision.

Cardiac glycosides
Administered concurrently, high-dose calcium supplements can act synergistically with these drugs, which may induce arrythmias and potentiate their toxicity — use this combination with caution.

Corticosteroids
Both oral and long-term inhaled corticosteroids inhibit vitamin D-mediated calcium absorption: overall levels of calcium may be decreased — ensure adequate calcium intake and monitor for signs and symptoms of deficiency. Consider supplementation with long-term drug therapy.

Etidronate
Calcium may reduce drug absorption; however, adequate calcium is required for optimal drug effects — separate doses by at least 2 hours.

Excess dietary fat
This increases urinary excretion of calcium — ensure adequate calcium intake and monitor for signs and symptoms of deficiency.

Excess fibre, including guar gum
May simply delay or decrease absorption of calcium — separate doses by at least 2 hours.

Levothyroxine
Calcium administered concurrently may reduce drug absorption — separate doses by at least 4 hours.

Lysine
Additive effects may occur as lysine enhances intestinal absorption and reduces renal excretion of calcium — potentially beneficial interaction.

Magnesium
Magnesium decreases calcium absorption as they compete for the same absorption pathway — separate doses by at least 2 hours.

Oestrogen and progesterone
Calcium supplementation in combination with these hormones will have an additive effect on minimising bone resorption in postmenopausal women — potential beneficial interaction, so consider increasing intake.

Phosphorus
Excess intake (soft drinks, meat consumption) can increase urinary excretion of calcium — ensure adequate calcium intake and monitor for signs and symptoms of deficiency.

Tetracyclines
Calcium supplements form complexes with these antibiotics and render 50% or more insoluble, therefore reducing the efficacy of the drug and absorption of calcium — separate doses by at least 2 hours.

Thiazide diuretics
These diuretics decrease urinary excretion of calcium. Monitor serum calcium and look for signs of hypercalcaemia, such as anorexia, polydipsia, polyuria, constipation and muscle hypertonia when using high-dose calcium supplements. Contributing risk factors are the presence of hyperparathyroidism or concurrent use of vitamin D.

Zinc
Calcium supplementation has been shown in some studies to increase faecal losses of zinc (McKenna et al 1997) — ensure adequate zinc intake and monitor for signs and symptoms of deficiency.

CONTRAINDICATIONS AND PRECAUTIONS
People with hyperparathyroidism, chronic renal impairment or kidney disease, sarcoidosis or other granulomatous diseases should only take calcium supplements under medical supervision. Calcium supplementation is contraindicated in hypercalcaemia.

PREGNANCY USE
Many trials have established the safety of calcium supplementation during pregnancy in doses up to 2000 mg elemental calcium per day.

PRACTICE POINTS/PATIENT COUNSELLING

- Calcium is an essential mineral required for the proper functioning of numerous intracellular and extracellular processes, including muscle contraction, nerve conduction, beating of the heart, hormone release, blood coagulation, energy production and maintenance of immune function.
- Low-calcium states are associated with several serious diseases such as colorectal cancer, osteoporosis types I and II, hypertension, preeclampsia and eclampsia.
- Although supplementation is traditionally used to correct or avoid deficiency states, research has also shown a role in the prevention of osteoporosis, preeclampsia and management of numerous disease states
- Clinical studies show that calcium supplementation may have benefits in premenstrual syndrome, hypertension, weight loss and reducing incidence of some cancers.
- Calcium can interact with numerous drugs and should be used with caution by people with renal disease or hyperparathyroid conditions.

PATIENTS' FAQs

What will this supplement do for me?

Calcium is essential for health and wellbeing. Although used to prevent or treat deficiency states, and primarily associated with BMD, it is also beneficial in a wide range of conditions such as prevention of preeclampsia, premenstrual syndrome, some forms of hypertension, maintenance of fetal growth, treatment of lead toxicity and PMS. It is considered to be a critical nutrient in pregnancy.

When will it start to work?

This will depend on the indication it is being used to treat; however, in most instances long-term administration is required (i.e. months to years).

Are there any safety issues?

In very high doses, calcium supplements can cause some side effects, including constipation, but generally calcium is considered very safe and has a wide therapeutic range. High-dose supplements should not be used by people taking some medications. Caution should also be exercised with high doses in individuals with preexisting cardiovascular disease. (See *Significant interactions* above for specific information.)

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Calendula

HISTORICAL NOTE Calendula is indigenous to Eastern Europe and the Mediterranean where its medicinal value has been respected since ancient times. Calendula was popular in Ancient Greece and in earlier Indian and Arabic cultures. It has been a common garden plant since the 12th century and it is mentioned in several older herbals. The name calendula comes from the Latin *calends*, meaning the first day of the month, referring to the plant's near continual flowering habit.

COMMON NAME
Marigold

OTHER NAMES
Pot or garden marigold, gold-bloom, holligold.

Field marigold (*Calendula arvensis*) is also used medicinally for the same indications because it has similar constituents.

BOTANICAL NAME/FAMILY
Calendula officinalis (family Asteraceae [Compositae or Daisy])

PLANT PARTS USED
The flowers are primarily used, but the stems, younger leaves, seeds and roots all have medicinal properties.

CHEMICAL COMPONENTS
The major constituents are triterpene saponins (2–10%) based on oleanolic acid and flavonols (3-O-glycosides of isorhamnetin and quercetin), including astragalin, hyperoside, isoquercitrin and rutin, as well as the carotenoids flavoxanthin and auroxanthin (Bako et al 2002). The triterpendiol esters faradiol laurate, faradiol myristate and faradiol palmitate have been identified as the major active compounds, which are also used as marker compounds for standardisation of calendula extracts (Hamburger et al 2003, Zitterl-Eglseer et al 2001). The terpenoids faradiol, amidiol and calenduladiol have been shown to have anti-inflammatory activity (Neukirch et al 2005).

Other constituents include essential oil, sesquiterpenes, including caryophyllene, and triterpenes, including amyrins, lupeol and lupenone. Calendula also contains polysaccharides (WHO 2003), as well as minerals such as calcium, sodium, potassium, magnesium, iron, copper and manganese (Ahmed et al 2003).

MAIN ACTIONS

Antimicrobial
Hydro-alcoholic extracts have been shown to have antibacterial, antiviral and antifungal activities. The in vitro antifungal activity of calendula flower extracts has been investigated against *Aspergillus niger*, *Rhizopus japonicum*, *Candida albicans*, *C. tropicalis* and *Rhodotorula glutinis*. Calendula extract showed a high degree of activity against all fungi and the inhibitory effect was comparable to that of standard antifungals (Kasiram et al 2000). A flower extract has been shown to inhibit trichomonas. The oxygenated terpenes are thought to be the main active compounds (Gracza & Szasz 1968, Samochowiec et al 1979). A 70% hydro-alcoholic extract demonstrated virucidal activity against influenza virus and suppressed the growth of HSV (Bogdanova et al 1970). Calendula flower extract has also been shown to possess anti-HIV and anti-EBV activity in vitro (Kalvatchev et al 1997, Ukiya et al 2006).

Promotes wound healing
An ointment containing 5% calendula flower extract, as well as an ointment containing two different fractions of calendula extract combined with allantoin, have been shown to stimulate physiological regeneration and epithelialisation in experimentally induced surgical wounds. The effect is thought

to be due to more intensive metabolism of glycoproteins, nucleoproteins and collagen proteins during regeneration of the tissues (Klouchek-Popova et al 1982).

Anti-inflammatory

Anti-inflammatory activity has been demonstrated in several animal models. Pretreatment with an 80% hydro-alcoholic extract reduced carrageenan-induced rat paw oedema at a dose of 100 mg extract/kg. Endomethacin 5 mg/kg was shown to be 4-fold more potent in the same experiment (Mascolo et al 1987). Both a 70% hydro-alcoholic extract and a CO_2-extract have been shown to inhibit experimentally induced inflammation and oedema. The triterpenoids were shown to be the main active anti-inflammatory compounds, with the faradiol monoester appearing to be the most relevant compound due to its quantitative prevalence (Della et al 1994). A freeze-dried extract of calendula was found to suppress both the inflammatory effect and leukocyte infiltration in an inflammatory model induced by the simultaneous injection of carrageenan and PGE_1 (Shipochliev et al 1981).

Ten triterpenoid glycosides (including four new compounds) were isolated from calendula and tested for anti-inflammatory activity. Of these, nine were found to be effective against 12-O-tetradecanoylphorbol-13-acetate–induced inflammation in mice (Ukiya et al 2006).

OTHER ACTIONS

Reduces oedema

Oral administration of a triterpene-containing fraction prevented the development of ascites and increased survival time compared with controls in mice inoculated with a carcinoma (Boucaud-Maitre et al 1988). The main triterpendiol esters of calendula, the faradiol esters, have been shown to possess anti-oedema activity by inhibiting croton oil-induced oedema of the mouse ear (Zitterl-Eglseer et al 1997).

Immunomodulation

Isolated polysaccharides have been shown to stimulate phagocytosis of human granulocytes (Varljen et al 1989, Wagner et al 1985). A 70% ethanol extract of calendula was shown to completely inhibit the proliferation of lymphocytes in the presence of phytohaemagglutinin in vitro (Amirghofran et al 2000).

Antioxidant

Calendula has free radical scavenging and antioxidant activity, with aqueous extracts having greater activity than methanolic extracts, with antioxidant activity being related to the total phenolic content and flavonoid content (Cetkovic et al 2004).

The butanolic fraction of a calendula extract has been shown to reduce superoxide and hydroxyl radicals, suggesting a free radical scavenging effect. Lipid peroxidation in liver microsomes is also reduced (Cordova et al 2002). Isorhamnetin glycosides isolated from calendula have been shown to inhibit the activity of lipo-oxygenase (Bezakova et al 1996).

Antispasmodic activity

Calendula has demonstrated anti-spasmodic activity in isolated gut preparations (Bashir et al 2006). These effects appeared to be due to calcium channel blocking and cholinergic activity.

Hypoglycaemic activity

A methanolic extract and its butanol-soluble fraction have been found to have hypoglycaemic and gastroprotective effects and to slow gastric emptying. From the butanol-soluble fraction, four new triterpene oligoglycosides, calendasaponins A, B, C and D, were isolated, together with eight known saponins, seven known flavonol glycosides, and a known sesquiterpene glucoside. Their structures were elucidated on the basis of chemical and physicochemical evidence. The principal saponin constituents, glycosides A, B, C, D and F, exhibited potent inhibitory effects on an increase in serum glucose levels in glucose-loaded rats, gastric emptying in mice, and ethanol and indomethacin-induced gastric lesions in rats (Yoshikawa et al 2001).

Hypolipidaemic activity

Oral administration of an isolated saponin fraction has been shown to reduce serum lipid levels in hyperlipidaemic rats (ESCOP 1996).

Hepatoprotective

Calendula extracts have been shown to have hepatoprotective effects on rat hepatocytes both in vitro and in vivo (Barajas-Farias et al 2006, Rusu et al 2005), with cytotoxic and genotoxic effects being evident at very high doses (Barajas-Farias et al 2006, Perez-Carreon et al 2002).

CLINICAL USE

Calendula is generally used in the treatment of inflammatory skin disorders or inflammation of the mucosa and as an aid to wound healing (Blumenthal et al 2000, ESCOP 1996). It is used both internally and topically for a variety of indications.

Wounds and burns

Historically, calendula flower preparations have been used to accelerate the healing of wounds, burns, bruises, grazes and minor skin infections. In recent times, it has been investigated for its effects on wound healing in a variety of experimental models and clinical studies as either a stand-alone topical treatment or in combination with other ingredients.

In an RCT involving 254 patients treated with adjuvant radiotherapy for breast cancer, topical treatment with calendula to the irradiated skin was found to be significantly more effective than trolamine in reducing acute dermatitis, with patients receiving calendula having less frequent interruption of radiotherapy and significantly reduced radiation-induced pain (Pommier et al 2004). In another controlled trial involving 34 patients with venous leg ulcers, a calendula extract applied twice daily for 3 weeks was found to produce a statistically significant acceleration in healing compared to a saline solution (Duran et al 2005).

Calendula ointment (8%, 1:10 tincture in 70% alcohol) is a useful adjuvant treatment during cosmetic surgery, according to a study of 19 cleft-lip patients with discoloured scar tissue. Pretreatment with the calendula ointment under a gauze dressing every evening for 1 month improved the results of dermatography, a refined tattooing technique used to improve the appearance of scars (Van der Velden & Van der Dussen 1995). Another clinical study used a mixture of chlorhexidine acetate and a 2% calendula extract as a haemostatic aerosol, producing good results (Garg & Sharma 1992).

A larger, open, randomised parallel study of 156 patients in four burn centres in France compared the effects of three different topical ointments (calendula, a proteolytic ointment and vaseline) on the management of second and third degree burns. A thick layer of the test ointment was applied daily under a closed dressing until grafting or spontaneous healing occurred and effectiveness was evaluated between the 8th and 12th day of treatment. Failure was defined as the presence of an eschar, local infection, premature treatment discontinuation or failure to complete the study. A marginally significant difference in favour of calendula over vaseline was observed and calendula was significantly better tolerated than the other treatments (Lievre et al 1992).

Prophylactic treatment with calendula ointment has also been used successfully to reduce the incidence and severity of bedsores in an open multicentre study. In other studies, positive results have been demonstrated in the treatment of poor venous return associated with ulcers, thrombophlebitis and other cutaneous changes such as inflammation, cracks and eczema (Issac 1992).

In practice, calendula is sometimes used together with St John's wort for stronger effects. The combination of *Calendula arvensis* (field marigold) and *Hypericum perforatum* oils has been shown to improve the epithelial reconstruction of surgical wounds in childbirth with caesarean section (Lavagna et al 2001).

A combination of calendula, *Arctium lappa* and *Geranium robertianum* has also been shown to improve healing of ulceration in 52 patients suffering herpetic keratitis compared with treatment with acyclovir alone (Corina et al 1999).

Commission E approves the external use of calendula for poorly healing wounds and leg ulcers (Blumenthal et al 2000).

Gastrointestinal inflammatory disorders (in combination)

An oral mixture of *Symphytum officinalis* (comfrey) and calendula was beneficial in the treatment of duodenal ulcers and gastroduodenitis according to a study involving 170 patients. Of these, 137 were treated with the herbal combination and 33 also received an antacid. A dramatic 90% of treated patients became pain free and 85% had a reduction in dyspeptic complaints. Gastric acidity showed a statistically insignificant tendency to decrease in both groups. Gastroscopy later revealed that the ulcers had healed in 90% of patients (Chakurski et al 1981). Interestingly, a smaller study conducted by the same researchers involving only 32 patients with the same condition failed to detect a beneficial effect (Matev et al 1981).

A further study by the same authors found another mixture containing calendula to be beneficial in the treatment of chronic colitis. A combination of *Taraxacum officinale*, *Hypericum perforatum*, *Melissa officinalis*, *Calendula officinalis* and *Foeniculum vulgare* was shown to relieve the spontaneous and palpable pains along the large intestine in over 95% of the patients ($n = 24$) by day 15 of treatment. Defecation was normalised in patients with diarrhoea and constipated patients were successfully treated with the addition of *Rhamnus frangula*, *Citrus aurantium* and *Carum carvi*. The pathological admixtures in faeces disappeared (Chakurski et al 1981).

Although encouraging, the role of calendula as a stand-alone treatment is difficult to determine from these studies. Additionally, the oral ingestion of comfrey is not recommended due to potential hepatotoxic effects.

Gingivitis

Calendula has been shown in an open, clinical study to be beneficial in the treatment of chronic catarrhal gingivitis (Krazhan & Garazha 2001). Interestingly, calendula extract failed to show any significant activity in vitro against common oral microorganisms in a second study that tested it against the saliva and dental plaque from 20 infants (Modesto et al 2000); however, a homeopathic preparation of calendula has been found to inhibit *Streptococcus mutans* (Giorgi et al 2004).

Commission E approves the internal and topical use of calendula flowers for inflammation of the oral and pharyngeal mucosa (Blumenthal et al 2000).

NAPPY RASH

Efficacy and safety of two baby creams in nappy rash

In a postmarketing surveillance study (Guala et al 2007), 82 infants aged between 3 days and 48 months were randomised to receive either calendula cream (Weleda) or Babygella for treatment of their nappy rash. Both preparations were judged by physicians and mothers as useful, however mothers tended to describe the calendula cream more frequently than Babygella as very good rather than satisfactory. The calendula cream also contained other anti-inflammatory and healing ingredients such as chamomile and zinc, making the contribution of calendula hard to judge.

OTHER USES

The British Herbal Pharmacopoeia recommends calendula for gastric and duodenal ulcers, amenorrhoea, dysmenorrhoea and epistaxis (BHMA 1983). Topically it is recommended for leg ulcers, varicose veins, haemorrhoids, eczema and proctitis. The specific indications are for enlarged or inflamed lymphatic nodes, sebaceous cysts, duodenal ulcers, and acute and chronic inflammatory skin conditions. Its

styptic activity makes it a popular topical treatment for bleeding.

DOSAGE RANGE

- Dried herb: 1–2 g as an infusion daily in divided doses.
- Liquid extract (1:2): 15–30 mL/week for internal use or 1.5–4.5 mL/day in divided doses. Dilute 1:3 for external application.
- Tincture (1:5): 0.3–1.2 mL three times daily.
- Calendula oil can be produced by steeping fresh flowers in vegetable oil for 1 week. Strain before use.

TOXICITY

Calendula has low toxicity. No symptoms of toxicity were found after long-term administration of a calendula extract in animal studies (Elias et al 1990, ESCOP 1996). A study evaluating an excessive dose (5 g/kg) in rats found no toxicity, however signs of liver and kidney burden were noted (Silva et al 2007). Calendula has been found to be neither mutagenic nor carcinogenic (Elias et al 1990).

ADVERSE REACTIONS

Irritant dermatitis from calendula has been reported (Paulsen 2002, Reider et al 2001) but is rare. Sesquiterpene lactones are the most important allergens present in Compositae species, but there are also a few cases of sensitisation from a coumarin, a sesquiterpene alcohol and a thiophene (Paulsen 2002).

A study of over 1000 patients randomly chosen from several different patch test clinics identified only one who reacted to calendula (Bruynzeel et al 1992). Patch test results need to be carefully interpreted because false positives can occur, as the following case shows. A 35-year-old woman with recalcitrant atopic dermatitis, with a positive patch-test reaction to Compositae mix, was told she was allergic to calendula. However, it turned out that she followed a self-devised diet consisting largely of food products of the Compositae family (which includes lettuces and artichoke). On excluding these foods her skin condition improved quickly. This case report underscores the difficulty in determining the relevance of positive patch tests, and shows that thorough analysis of positive patch tests, by both patient and physician, may reveal unexpected or less common sources of contact allergens (Wintzen et al 2003).

SIGNIFICANT INTERACTIONS

Controlled studies are not available to assess the interaction potential of calendula.

CONTRAINDICATIONS AND PRECAUTIONS

Use with caution in patients with confirmed allergy to herbs or foods from the Compositae family.

PREGNANCY USE

Insufficient reliable information available to assess safety.

PATIENTS' FAQs

What will this herb do for me?

Calendula is used for inflammatory skin conditions, including poor wound healing, burns and ulcers, due to its non-irritant, antiseptic and healing properties. Internally it is used for inflammation and ulceration of the digestive tract.

When will it start to work?

Topical effects are quickly established and should improve with continuous use. Internal use may take longer.

Are there any safety issues?

Although there have been some reports of allergic reactions to calendula, these are very rare. Calendula is generally well tolerated by children and adults.

PRACTICE POINTS/PATIENT COUNSELLING

- Calendula has antimicrobial and anti-inflammatory activity and promotes wound healing.
- European text books recommend calendula for inflammation of the skin, poorly healing wounds, bruises, boils, rashes, bed sores, dermatitis resulting from chilblains, wound healing after amputations, cracked nipples during pregnancy and lactation, acne, sunburns, burns and nappy rashes. Calendula is also indicated for pharyngitis and tonsillitis (Bisset 1994, Bruneton 1999, Evans 2002, Issac 1992).
- There is some evidence from clinical trials that calendula may be beneficial in the treatment of burns, wounds and gastrointestinal inflammation and ulceration.
- People who are sensitive or allergic to foods or plants from the Compositae family should use calendula with caution.

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Carnitine

BACKGROUND AND RELEVANT PHARMACOKINETICS

Carnitine was discovered in 1905, although its role in metabolism was only described in the mid 1950s and deficiency symptoms outlined in 1972. It is a trimethylated amino acid, roughly similar in structure to choline, that is ingested through the diet and also synthesised from lysine and methionine in the body. To do this, a large number of cofactors are required, such as *S*-adenosyl methionine (SAMe), methionine, magnesium, vitamins C, B_6, B_2, B_3, iron, alpha-ketoglutarate and oxygen (Kelly 1998).

Clinical note — Acetyl-L-carnitine shows promise as a strong therapeutic agent

Acetyl-L-carnitine, an ester form of L-carnitine, has also been investigated for its use in the treatment of Alzheimer's disease (Brooks et al 1998, Pettegrew et al 1995, Sano et al 1992, Thal et al 1996); depression (Garzya 1990), physical and mental fatigue, cognitive status and physical function in the elderly (Malaguarnera et al 2008); diabetic (De Grandis & Minardi 2002), peripheral (Onofrj et al 1995), and antiretroviral toxic neuropathy (Youle & Osio 2007) as well as prevention of neuropathy in chemotherapy (Bianchi et al 2005, Maestri et al 2005). It has also been researched for fatigue in multiple sclerosis (Tomassini et al 2004); fibromyalgia syndrome (Rossini et al 2007), Peyronie's disease (Biagiotti & Cavallini 2001), degenerative cerebellar ataxia (Sorbi et al 2000) and cognitive disturbances in chronic alcoholics (Tempesta et al 1990).

Dietary carnitine is absorbed in the intestine via a combination of active transport and passive diffusion (Li et al 1992). Mucosal absorption is saturated at around 2 g carnitine (Harper et al 1988), however more recent data suggest that mean plasma concentrations do not increase with doses over 0.5 g three times daily (Bain et al 2006). The bioavailability of carnitine is difficult to establish as reports vary widely from 16 to 87% (Harper et al 1988, Rebouche & Chenard 1991). Peak blood levels occur 3.5 hours after digestion and excretion is primarily via the kidneys (Bach et al 1983).

CHEMICAL COMPONENTS

L-Carnitine is the form most commonly used. As the D form is not biologically active, there is concern that it might interfere with the use of the L isomer by competitive inhibition and thus cause L-carnitine deficiency (Tsoko et al 1995).

FOOD SOURCES

Red meat is the richest dietary source. Vegetarian sources include avocado and tempeh (Hendler & Rorvik 2001). Human colostrum also contains carnitine (Wahlqvist 2002).

DEFICIENCY SIGNS AND SYMPTOMS

L-Carnitine deficiency leads to an accumulation of free fatty acids in the cell cytoplasm and of acyl-coenzyme A (CoA) in the mitochondria. This produces a toxic effect and disturbs fatty acid use for energy production (Kletzmayr et al 1999).

Deficiency symptoms (Kelly 1998) include the following:

- hypoglycaemia
- progressive myasthenia
- hypotonia
- fatigue
- cardiomyopathy
- congestive heart failure
- encephalopathy
- hepatomegaly
- neuromuscular disorders
- failure to thrive in infants
- muscle fatigue and cramps
- myoglobinaemia following exercise.

Elevation of triglycerides may also occur due to the role of carnitine in fatty acid metabolism.

Clinical note — Primary carnitine deficiency: an uncommon inherited disorder

Primary carnitine deficiency is an uncommon inherited disorder, related to a functional defect in plasma membrane carnitine transport in muscle and in the kidneys. These conditions have been classified as either systemic or myopathic (Evangeliou & Vlassopoulos 2003, Matera et al 2003). Systemic carnitine deficiency is reflected by low levels of carnitine in plasma and muscle and may result in cardiomyopathy, skeletal myopathy, hypoglycaemia and hyperammonaemia (Hendler & Rorvik 2001). Myopathic deficiency presents with normal plasma but low muscle carnitine levels and is a defect of carnitine transport across the muscle cell membrane (Winter et al 1987).

Primary deficiency

People at risk of primary deficiency are vegetarians, preterm infants and infants receiving a carnitine-free formula, and those with an inherited functional defect.

Secondary deficiency

Secondary carnitine deficiency is associated with several inborn errors of metabolism and acquired medical or iatrogenic conditions, such as the following (Evangeliou & Vlassopoulos 2003):

- genetic defects of metabolism, including methylmalonic aciduria, cytochrome C oxidase deficiency, fatty acyl-CoA dehydrogenase deficiency
- medications (Patients taking valproate and the anti-HIV drug azidothymidine are at risk.)
- dialysis (Carnitine depletion in haemodialysis patients is caused by insufficient carnitine synthesis and particularly by loss through the dialytic membranes. Many studies have shown that L-carnitine supplementation leads to improvements in several complications seen in uraemic patients, including cardiac complications, impaired exercise and functional capacities, muscle symptoms, increased symptomatic intradialytic hypotension, and erythropoietin-resistant anaemia, normalising the reduced carnitine palmitoyl transferase activity in red cells [Matera et al 2003].)
- liver disease, which impairs the last stage of carnitine synthesis, resulting in deficiencies in cardiac and skeletal muscle
- chronic renal failure and renal tubular disorders, in which excretion of carnitine may be excessive
- intestinal resection
- coeliac disease (A case report exists of a 48-year-old man developing encephalopathy due to carnitine deficiency as a result of coeliac disease [Karakoc et al 2006]. In patients with idiopathic dilated cardiomyopathy associated with coeliac disease, a gluten-free diet has been shown to increase serum carnitine levels [Curione et al 2005].)

- preterm neonates (Develop carnitine deficiency due to impaired proximal renal tubule carnitine re-absorption and immature carnitine biosynthesis.)
- hypopituitarism (Martindale 1999)
- adrenal insufficiency (Hendler & Rorvik 2001)
- advanced AIDS (Hendler & Rorvik 2001)
- vitamin C deficiency (Hendler & Rorvik 2001)
- other chronic conditions — diabetes mellitus, heart failure, Alzheimer's disease.

MAIN ACTIONS

Carnitine is involved in a myriad of biochemical processes important for health and wellbeing.

Cellular energy production

Carnitine assists the transport of fat across cell membranes in muscle tissue for use as an energy source (Wahlqvist 2002). It is essential for mitochondrial fatty acid oxidation, which is the primary fuel source for the heart and skeletal muscles and therefore required for proper functioning (Evangeliou & Vlassopoulos 2003, Kelly 1998). This process is also required in order to maintain CoA levels. The combination of exercise training and L-carnitine (4 g/day) supplementation does not appear to augment fatty acid-binding protein (FABPc) expression and beta-hydroxyacyl CoA dehydrogenase (beta-HAD) activity in human skeletal muscle, indicating that combined treatment does not exert an additive effect in fat metabolism and would thus be unlikely to enhance exercise performance (Lee et al 2007).

Improves blood sugar control

Administration of L-carnitine reduces insulin secretion and improves peripheral glucose use (Grandi et al 1997) and tissue insulin sensitivity (Negro et al 1994).

Cellular function and integrity

Carnitine is involved in the protection of membrane structures, stabilising a physiological CoA-sulfate hydrate/acetyl-CoA ratio, and reduction of lactate production (Matera et al 2003).

OTHER ACTIONS

Increases male fertility

Based on the high concentrations of L-carnitine in the epididymis, it has been proposed that spermatozoa, which require beta oxidation for energy, may require L-carnitine for proper maturation (Lenzi et al 1992). Human trials have found carnitine therapy (2–3 g/day) to be effective in increasing semen quality, sperm concentration and total and forward sperm motility, especially in groups with lower baseline levels (Lenzi et al 2003). One trial also reported that improvements in sperm motility were only observed in the presence of normal mitochondrial function, determined by phospholipid hydroperoxide glutathione peroxidase levels (Garolla et al 2005).

Some studies suggest that a combination of L-carnitine (LC) and acetyl-L-carnitine (ALC) may provide benefit for the treatment of idiopathic asthenospermia and improve semen quality (Cheng & Chen 2008). However, a small RCT using L-carnitine (2000 mg) and L-acetyl-carnitine (1000 mg) per day for 24 weeks failed to demonstrate improvements in sperm motility or total motile sperm counts in men with idiopathic asthenospermia (Sigman et al 2006). A meta-analysis comparing LC and/or LAC therapy to placebo found significant improvements in pregnancy rate ($P < 0.0001$), total sperm motility ($P = 0.04$), forward sperm motility ($P = 0.04$) and atypical sperm cells ($P < 0.00001$) but not sperm concentration or semen volume (Zhou et al 2007).

Antioxidant

Carnitine acts as an antioxidant in the cell membrane, preventing protein oxidation and pyruvate and lactate oxidative damage (Peluso et al 2000). In vitro studies suggest a dose-dependent inhibition of lipid peroxidation of linoleic acid emulsion superior to (alpha)-tocopherol. In addition, L-carnitine may have an effect on superoxide anion radical scavenging, hydrogen peroxide scavenging, total reducing power and metal chelating on ferrous ions (Gulcin 2006).

Prevents apoptosis

In vitro and animal studies show that L-carnitine can prevent apoptosis of skeletal muscle cells (Vescovo et al 2002). In patients with HIV it decreases numbers of $CD4^+$ and $CD8^+$ cells undergoing apoptosis, and significantly increases $CD4^+$ counts (Moretti et al 2002).

Neuroprotective

Animal studies have demonstrated a reduction in mortality and neuronal degeneration in experimentally induced neurotoxicity (Binienda et al 2004) and a reduction in hypoglycaemia-induced neuronal damage (Hino et al 2005) in rats that were pretreated with carnitine. In vitro studies suggest that the anti-apoptotic and antioxidant actions of L-carnitine contribute to the neuroprotective effect (Ishii et al 2000, Tastekin et al 2005).

Lipid-lowering

The role of carnitine in fatty acid metabolism suggests a potential role in hyperlipidaemia. Several studies have indicated that oral L-carnitine significantly reduces lipoprotein-a levels; however, effects on other lipids are inconsistent. According to human trials the addition of L-carnitine (2 g/day) to simvastatin therapy (20 mg/day) appears to lower lipoprotein-a serum levels in patients with type 2 diabetes mellitus (Solfrizzi et al 2006). In a separate placebo-controlled, double-blind randomised study L-Carnitine (2 g/day) significantly reduced serum lipoprotein-a levels in 77.8% of subjects receiving active treatment after 12 weeks. No significant change was observed in other lipid parameters (Sirtori et al 2000). L-Carnitine (2 g/day) was also shown to significantly lower lipoprotein-a levels at 3 and 6 months in a double-blind placebo-controlled trial of 94 hypercholesterolaemic patients with newly diagnosed type 2 diabetes (Derosa et al

2003). In a trial of children with hyperlipidaemia, lipoprotein-a levels were only reduced in those with type II homozygotes and other lipid parameters worsened (Gunes et al 2005).

L-Carnitine has also been shown to decrease apolipoprotein B levels in paediatric peritoneal dialysis patients (Kosan et al 2003). A study of elderly people taking L-carnitine (2 g twice daily) demonstrated improvements in total serum cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, apoproteins A1 and B at 30 days (Pistone et al 2003). Animal studies have also suggested the potential for carnitine to lower triglyceride levels (Eskandari et al 2004); however, clinical trials using oral doses in type 2 diabetes have indicated an increase in triglycerides (Rahbar et al 2005). Further human trials are required to confirm which population groups may benefit from carnitine supplementation.

CLINICAL USE

Carnitine supplementation may be administered as intravenous or oral doses. This review will only focus on oral supplementation as this is the form generally used by the public and available over the counter.

Treatment of deficiency

L-Carnitine supplementation is traditionally used to treat or prevent deficiency. It is indicated in primary L-carnitine deficiency and secondary deficiency due to inborn errors of metabolism or haemodialysis. L-Carnitine 50–200 mg/kg/day has been shown to normalise plasma carnitine levels within 10 days (Campos et al 1993).

Apnoea of prematurity

Preterm neonates develop carnitine deficiency due to impaired proximal renal tubule carnitine re-absorption and immature carnitine biosynthesis (Evangeliou & Vlassopoulos 2003) and are at risk of developing apnoea of prematurity. Despite a promising preliminary study, a blinded, randomised, placebo-controlled study found that infants who received supplemental carnitine did not demonstrate any reduction in apnoea of prematurity, days requiring ventilator or nasal continuous positive airway pressure, or the need for supplemental oxygen therapy (O'Donnell et al 2002). In a RCT premature neonates supplemented with carnitine (20 mg/kg/day) gained weight more rapidly and showed improvement in periodic breathing compared to placebo although other respiratory markers were unaffected (Crill et al 2006). A 2004 Cochrane review was unable to locate studies of significant quality to confirm any effects (Kumar et al 2004a). Further studies are needed to determine the role of this treatment in clinical practice as present evidence does not support its use (Kumar et al 2004b).

Cardiovascular disease

L-Carnitine supplementation in doses ranging from 2 g to 4 g/day has been investigated in a number of controlled studies involving subjects with angina, heart failure, cardiogenic shock, cardiomyopathy and post myocardial infarction. Overall, positive results have been obtained and reduced mortality reported for some populations.

Chronic stable angina

Controlled studies indicate that L-carnitine supplements increase exercise tolerance and reduce frequency of angina attacks, enabling some patients to reduce nitrate requirements.

One RCT of 47 patients with chronic stable angina found that 2 g L-carnitine taken daily for 3 months moderately improved the duration of exercise and the time taken for ST changes to recover to baseline (Iyer et al 2000). This study confirmed the results of an earlier multicentre, double-blind, randomised, placebo-controlled crossover trial that examined the effects of L-carnitine 1 g twice daily for 4 weeks in 44 men with stable chronic angina (Cherchi et al 1985). This study showed that active treatment resulted in increased exercise tolerance and reduced ECG indices of ischaemia in stable effort-induced angina. A meta-analysis also highlighted a significant reduction in the number of angina attacks and nitrate requirements with doses of 2 g/day (Fernandez & Proto 1992).

Post-myocardial infarction (MI)

L-carnitine supplementation may lead to a reduction in early mortality (assessed at day 5) without affecting the risk of death and heart failure at 6 months in patients with anterior acute MI (Tarantini et al 2006). A dose of 4 g/day L-carnitine over 12 months improved quality of life and increased life expectancy in patients who had suffered an MI, according to a controlled study (Davini et al 1992). This included an improvement in heart rate, systolic arterial pressure, a decrease in anginal attacks, and improvement in the lipid profile. Changes were also accompanied by lower mortality in the treated group (1.2% vs 12.5% in the control group).

In a randomised, double-blind placebo-controlled trial, the effects of oral L-carnitine (2 g/day) for 28 days were assessed in patients with suspected acute MI. Total cardiac events, including cardiac deaths and non-fatal infarction, were 15.6% in the carnitine group and 26.0% in the placebo group. Angina pectoris (17.6% vs 36.0%), New York Heart Association class III or IV heart failure plus left ventricular enlargement (23.4% vs 36.0%) and total arrhythmias (13.7% vs 28.0%) were significantly less in the carnitine group compared with placebo (Singh et al 1996).

Cardiomyopathy

Cardiomyopathy appears to cause leakage of carnitine from heart stores, which may make cardiac tissue vulnerable to damage; however, it is unclear whether carnitine leakage is a cause or effect of cardiomyopathy (Baker et al 2005). Long-term placebo-controlled studies (10–54 months) using an oral dose of 2 g/day L-carnitine for treatment of heart failure caused by cardiomyopathy found a statistically significant advantage in survival rates with carnitine treatment (Rizos 2000). In patients with idiopathic dilated cardiomyopathy associated with coeliac disease, a gluten-free diet has been shown to increase serum carnitine levels (Curione et al 2005).

Cardiogenic shock

Several studies confirm the role of L-carnitine in the reversible phase of cardiogenic shock in terms of enzymic protection in the course of cellular oxidative damage. This has been reflected in improved survival rates (Corbucci & Lettieri 1991, Corbucci & Loche 1993).

Congestive heart failure

In congestive heart failure a specific myopathy secondary to myocyte apoptosis triggered by high levels of circulating TNF-alpha has been described. The role of carnitine in preventing apoptosis in skeletal muscle and reducing TNF-alpha provides a theoretical basis for its use in the treatment of myopathy associated with congestive heart failure (Vescovo et al 2002).

Myocarditis resulting from diphtheria

Two studies using D,L-carnitine (100 mg/kg/day in two divided doses orally for 4 days) found a reduction in the incidence of, and mortality from, myocarditis in diphtheria (Ramos et al 1984, 1992).

Non-ST elevation acute coronary syndrome (NSTEMI)

In a RCT 96 patients with NSTEMI were randomised to treatment or control group. All patients received percutanenous coronary intervention within 24 h from the onset of chest pain. The treatment group also received L-carnitine (5 g IV bolus followed by 10 g/day IV infusion for 3 days) and demonstrated significantly lower levels of cardiac markers (creatine kinase-MB and troponin-I) (Xue et al 2007).

Peripheral vascular disease

Due to its anti-ischaemic activity, L-carnitine supplements have also been used in peripheral vascular disease. A double-blind crossover study supports this use, finding L-carnitine supplements (2 g/day) taken for 3 weeks increased walking time in people with peripheral vascular disease (Brevetti et al 1988). A derivative of L-carnitine, known as propionyl-L-carnitine, taken for 6 months (2 g/day orally) has also demonstrated significant improvements in walking distance and speed in patients with claudication (Hiatt et al 2001).

Hyperthyroidism

Considering that this condition is associated with reduced body stores of carnitine and that L-carnitine is a peripheral antagonist of thyroid hormone action in some tissues according to in vivo studies, carnitine treatment has been investigated in hyperthyroidism.

One 6-month, randomised, double-blind placebo-controlled trial involving 50 women with induced suppression of thyroid-stimulating hormone showed that doses of 2 g or 4 g/day oral L-carnitine both reversed and prevented symptoms of the disease and had a beneficial effect on bone mineralisation (Benvenega et al 2001).

Male fertility

Some studies suggest that a combination of L-carnitine (LC) and acetyl-L-carnitine (ALC) may provide benefit for the treatment of idiopathic asthenospermia and improve semen quality (Cheng & Chen 2008). A placebo-controlled, double-blind crossover trial of 100 infertile males (aged 20–40 years) found that L-carnitine therapy (2 g/day) was effective in increasing semen quality, sperm concentration and total and forward sperm motility, especially in groups with lower baseline levels (Lenzi et al 2003). The positive effects on sperm motility have also been shown in previous trials using L-carnitine 3 g/day (Costa et al 1994, Vitali et al 1995). In a later trial, improvements in sperm motility were only observed in the presence of normal mitochondrial function, determined by phospholipid hydroperoxide glutathione peroxidase levels (Garolla et al 2005). A meta-analysis comparing LC and/or ALC therapy to placebo found significant improvements in pregnancy rate ($P < 0.0001$), total sperm motility ($P = 0.04$), forward sperm motility ($P = 0.04$) and atypical sperm cells ($P < 0.00001$) but not sperm concentration or semen volume (Zhou et al 2007). One small RCT of 21 men (12 in the treatment group, 9 in the placebo group) with idiopathic asthenospermia showed that a combination of L-carnitine (2000 mg) and L-acetyl-carnitine (1000 mg) taken daily over 24 weeks failed to demonstrate improvements in sperm motility or total motile sperm counts (Sigman et al 2006).

Ergogenic aid

L-Carnitine is a popular supplement amongst athletes in the belief that it will increase performance and recovery. This concept is largely based on the fact that carnitine assists in the transport of fat across cell membranes in muscle tissue and is involved in cellular energy production. However, the combination of exercise training and L-carnitine (4 g/day) supplementation does not appear to augment fatty acid-binding protein (FABPc) expression and beta-hydroxyacyl CoA dehydrogenase (beta-HAD) activity in human skeletal muscle, suggesting that combined treatment does not exert an additive effect in fat metabolism and would thus be unlikely to enhance exercise performance (Lee et al 2007).

Carnitine reduces insulin secretion and significantly improves peripheral glucose use, when administered with glucose, according to human research (Grandi et al 1997). There is evidence that L-carnitine supplementation may increase maximal oxygen consumption, stimulate lipid metabolism and reduce post-exercise plasma lactate (Karlic & Lohninger 2004). A recent trial reported that acute intake of L-carnitine (2 g) one hour prior to exercise did not appear to affect metabolic or blood lactate values of badminton players, although there was a significant difference in exercise maximum heart rate in male participants ($P < 0.05$) (Eroglu et al 2008).

In a placebo-controlled crossover trial using an L-carnitine–L-tartrate (LCLT) supplement (2 g L-carnitine/day) for 3 weeks, researchers suggested that LCLT supplementation was effective in assisting recovery from high-repetition squat exercise (Volek et al 2002). A similar trial of the same dose and duration suggested that recovery from post-resistance-exercise may be mediated by upregulation of androgen

receptor content (Kraemer et al 2006). However, other clinical trials using 2 g L-carnitine twice daily for 3 months found no significant increase in muscle carnitine content, mitochondrial proliferation, or physical performance (Wachter et al 2002). Similarly a study using glycine propionyl-L-carnitine (GPLC, 1–3 g/day) for 8 weeks in conjunction with aerobic-exercise training failed to demonstrate improvement in muscle carnitine content, aerobic- or anaerobic-exercise performance (Smith et al 2008).

Ergogenic aid in cardiovascular disease

Trials in subjects with cardiovascular disorders have been more promising. This is supported by the clinical trial discussed earlier involving patients with chronic stable angina (Iyer 2000). In addition, a clinical trial using 1 g L-carnitine or placebo three times daily for 120 days has indicated a potential for improved performance and effort tolerance in patients with cardiac insufficiency (Loster et al 1999).

Ergogenic aid in chronic obstructive pulmonary disease (COPD)

Compared to placebo, L-carnitine (2 g/day) for 6 weeks can significantly improve inspiratory muscle strength (14 ± 5 vs 40 ± 14 cmH_2O) and exercise tolerance (walking test) (34 ± 29 vs 87 ± 30 m, $P < 0.05$) in COPD patients, as well as reducing lactate production (2.3 ± 0.7 vs 1.6 ± 0.7 mM, $P < 0.05$) (Borghi-Silva et al 2006).

OTHER USES

Fatigue

Chronic fatigue syndrome

Studies investigating whether people with CFS have lower levels of free L-carnitine have shown contradictory results (Jones et al 2005), and trials using L-carnitine supplementation in CFS have generally produced mixed results (Plioplys & Plioplys 1995, 1997, Soetekouw et al 2000). One randomised controlled trial did find that 1 g L-carnitine (three times daily) produced a significant clinical improvement, especially between the fourth and eighth week of treatment (Plioplys & Plioplys 1997).

Fatigue in cancer patients

In a trial of advanced cancer patients 76% were found to be carnitine deficient. In a subset of patients (those whose carnitine levels increase with supplementation) doses up to 3 g/day is deemed to be safe and may reduce fatigue (Cruciani et al 2006).

Fatigue in coeliac disease patients

L-Carnitine blood levels are low in coeliac disease patients most likely due to reduced OCTN2 levels (the specific carnitine transporter). In 60 coeliac disease patients, L-carnitine supplementation (2 g/day) for 180 days has been shown to be safe and effective in ameliorating fatigue measured by the Scott-Huskisson Visual Analogue Scale for Asthenia compared with placebo ($P = 0.0021$) (Ciacci et al 2007).

Attention deficit hyperactivity disorder

In a randomised, double-blind, placebo-controlled double-crossover trial, treatment with L-carnitine (100 mg/kg twice daily, maximum 4 g/day) over 24 weeks significantly decreased the attention problems, delinquency and aggressive behaviour in boys with ADHD (Van-Oudheusden & Scholte 2002). At 6-month follow-up 19 of 24 boys had responded to treatment as judged by parents and teachers.

Diabetes

Only high circulating serum insulin concentrations (≥ 90 mU/L) are capable of stimulating skeletal muscle carnitine accumulation (Stephens et al 2007). Carnitine is essential for lipid and carbohydrate metabolism, and correct metabolic control. It has been suggested that some people with diabetes may have reduced levels of total and free carnitine (Mamoulakis et al 2004). Administration of L-carnitine reduces insulin secretion and improves peripheral glucose use (Grandi et al 1997) and tissue insulin sensitivity (Negro et al 1994). Additionally in type 2 diabetes, L-carnitine (1 g 3 times daily) significantly lowers fasting plasma glucose, but may increase fasting triglycerides (Rahbar et al 2005). Although promising, further research is required to elucidate the possible benefits and safety of carnitine supplementation in this population.

Type 1 diabetes

L-Carnitine (2 g/m^2/day) in the early stage (stage 1a) of type 1 diabetes may improve nerve conduction velocity suggesting benefits for the treatment of sub-clinical neuropathy (Uzun et al 2005).

Haemodialysis

Carnitine depletion in haemodialysis patients is caused by insufficient carnitine synthesis and excessive loss through the dialytic membranes (Matera et al 2003). Carnitine supplementation has been approved by the US FDA for the treatment and prevention of carnitine depletion in dialysis patients. Supplementation in such patients is said to improve lipid metabolism, protein nutrition, antioxidant status and anaemia, and may reduce the incidence of intradialytic muscle cramps, hypotension, asthenia, muscle weakness and cardiomyopathy (Bellinghieri et al 2003). In maintenance haemodialysis patients L-carnitine supplementation (20 mg/kg) has been associated with protein-sparing effects during hyperinsulinaemia (Biolo et al 2008). L-carnitine supplementation (10 mg/kg orally), immediately after haemodialysis sessions 3 times/week for 12 months induced regression of left ventricular hypertrophy (LVH) in patients with normal cardiac systolic function undergoing haemodialysis (Sakurabayashi 2008).

However, the routine use of L-carnitine in dialysis patients to manage anaemia and refractory dialysis-associated hypotension is contentious and some authors believe that there is insufficient evidence to support this indication (Steinman et al 2003).

Hepatic encephalopathy

Hepatic encephalopathy (HE) is a major complication of cirrhosis. A recent systematic review suggested that L-acyl-carnitine is promising as a safe and effective treatment for HE (Shores & Keeffe 2008). Human trials have demonstrated a protective effect of L-carnitine (2 g twice daily) in ammonia-precipitated hepatic encephalopathy in cirrhotic patients at 30 days and more significantly at 60 days (Malaguarnera et al 2003).

Rett syndrome

A case is reported of a 17-year-old girl with Rett syndrome whose condition improved while using L-carnitine (50 mg/kg/day). Upon cessation, she relapsed, whereas re-establishing the treatment saw improvements after 1 week. More specifically, alertness increased, she started reaching for objects with both hands, and answered simple questions with one or two words. Interestingly, serum carnitine levels (free and total) were within normal limits before and after L-carnitine treatment (Plioplys & Kasnicka 1993). An 8-week randomised, placebo-controlled, double-blind crossover trial of L-carnitine has since been completed detecting improvements on the Hand Apraxia Scale and in the subjects' general wellbeing (Ellaway et al 1999).

Beta thalassaemia major

L-Carnitine appears to be a safe and effective adjunctive therapy in thalassaemia patients, especially younger patients. L-Carnitine therapy (50 mg/kg/day) for 6 months resulted in a significant increase in oxygen consumption, cardiac output and oxygen pulse at maximal exercise ($P < 0.001$, $P = 0.002$ and $P < 0.001$, respectively). There was also a significant increase in the blood transfusion intervals after L-carnitine administration ($P = 0.008$) (El-Beshlawy et al 2007). Additionally L-carnitine (100 mg/kg/day) for one month may prevent RBC deterioration in beta-thalassaemia major patients (Toptas et al 2006).

Ageing

In a randomised, double-blind, placebo-controlled trial of 84 elderly subjects (aged 70–92 years) who experienced onset of fatigue after slight physical activity, L-carnitine (2 g twice daily) for 30 days resulted in significant improvements in total fat mass, total muscle mass, lipid profiles, as well as overall improvements in physical and mental fatigue (Pistone et al 2003). Similarly in a placebo-controlled, randomised, double-blind, two-phase study of 66 centenarians with onset of fatigue even after slight physical activity, L-carnitine (2 g/day) treated centenarians showed significant improvements compared with the placebo group. Improvements included total fat mass (–1.80 vs 0.6 kg; $P < 0.01$), total muscle mass (3.80 vs 0.8 kg; $P < 0.01$), plasma concentrations of total carnitine (12.60 vs –1.70 micromol; $P < 0.05$), plasma long-chain acylcarnitine (1.50 vs –0.1 micromol; $P < 0.001$), and plasma short-chain acylcarnitine (6.0 vs –1.50 micromol; $P < 0.001$). Significant differences were also found in physical fatigue (–4.10 vs –1.10; $P < 0.01$), mental fatigue (–2.70 vs 0.30; $P < 0.001$), fatigue severity (–23.60 vs 1.90; $P < 0.001$), and Mini-Mental State Examination (MMSE) (4.1 vs 0.6; $P < 0.001$) (Malaguarnera et al 2007).

Animal studies have demonstrated that supplementation of carnitine (300 mg/kg/day) and lipoic acid (100 mg/kg/day) for 30 days protects mitochondria from ageing by raising mitochondrial energy production and reversing the age-associated decline in mitochondrial enzyme activity (Savitha et al 2005). Studies using standard oral doses of L-carnitine in humans are required to confirm these effects.

Weight loss

Carnitine is a popular supplement for weight loss when combined with an exercise program. This is based on its biochemical role in the production of energy from fatty acids. Carnitine deficiency impairs fatty acid beta-oxidation and may partly explain weight gain in valproate-treated patients. However, L-carnitine (15 mg/kg/day) for 26 weeks failed to improve weight loss outcomes in valproate-treated bipolar patients consuming an energy-restricted, low-fat diet (Elmslie et al 2006). Currently, one clinical trial that has investigated carnitine supplementation together with an aerobic training program failed to detect a significant effect on weight loss (Villani et al 2000).

DOSAGE RANGE

- Deficiency: L-carnitine 50–200 mg/kg/day.
- Most conditions: L-carnitine 2–4 g/day in divided dose.

Note: Maximum plasma concentration may be achieved at 500 mg. Therefore individual doses exceeding this level may not provide any additional benefits (Bain et al 2006). Larger doses should be divided.

According to clinical studies

- Cardiovascular disorders: 2 g/day for at least 3 months may improve exercise tolerance and recovery in people with conditions such as chronic stable angina and cardiac insufficiency, and may also reduce lipoprotein-a levels and improve peripheral vascular disease.
- Hyperthyroidism: 2–4 g/day in divided doses.
- Chronic fatigue syndrome: 1 g three times daily.
- Ergogenic aid: 2 g/day.
- Fertility: 2–3 g/day may be useful to increase sperm motility and concentration.
- Peripheral vascular disease: 2 g/day.
- COPD: 2 g/day.
- Thalassaemia (as adjunct): 50 mg/kg/day.
- Ageing (to reduce fatigue): 2 g daily or twice daily.

ADVERSE REACTIONS

Carnitine is well tolerated at recommended doses. Mild gastrointestinal symptoms including abdominal cramps, diarrhoea, nausea and vomiting, heartburn or gastritis may occur. Mild myasthenia has been reported in uraemic patients using the D,L form (Hendler & Rorvik 2001). Changes in body odour have also been noted (Sigma-Tau Pharmaceuticals 1999, Van-Oudheusden & Scholte 2002).

SIGNIFICANT INTERACTIONS

Anticoagulants

According to one case report, L-carnitine 1 g/day may potentiate the anticoagulant effects of acenocoumarol (also known as nicoumalone or acenocumarin) (Martinez et al 1993). Use this combination with caution. Monitor bleeding time and signs and symptoms of excessive bleeding.

Anticonvulsants (including valproate, phenobarbital, phenytoin, carbamazepine)

Trials with children and adults have shown a reduction in carnitine levels during anticonvulsant therapy (Hug et al 1991, Rodriguez-Segade et al 1989). A study evaluating carnitine deficiency in children and adolescents with epilepsy found 27.3% taking valproic acid and 14.3% taking carbamazepine showed low free-carnitine levels. Polytherapy, female sex, psychomotor or mental retardation and abnormal neurological examination appeared to increase the risk of hypocarnitinaemia. Patients taking topiramate or lamotrigine or on a ketogenic diet did not appear to be affected (Coppola et al 2006). L-Carnitine deficiency may cause or potentiate valproate toxicity and supplementation is known to reduce the toxicity of valproate, as well as symptoms of fatigue. In a trial using L-carnitine for acute valproate poisoning no adverse events were noted (LoVecchio et al 2005). Increased carnitine intake may be required with long-term therapy — potentially beneficial interaction under professional supervision.

Betamethasone

A RCT has shown that a combination of low-dose betamethasone (2 mg/day) and L-carnitine (4 g/5 days) was more effective in the prevention of respiratory distress syndrome (7.3% vs 14.5%) and death (1.8% vs 7.3%) in preterm infants than high-dose betamethasone given alone (8 mg/2 days) (Kurz et al 1993) — beneficial interaction possible under professional supervision.

Chemotherapy

Adriamycin (doxorubicin)

Animal studies suggest long-term carnitine administration may reduce the cardiotoxic side effects of adriamycin (Kawasaki et al 1996). A small randomised placebo-controlled trial attempted to determine these effects in humans, administering 3 g L-carnitine before each chemotherapy cycle, followed by 1 g L-carnitine/day during the following 21 days to the treatment group. The trial reported no cardiotoxicity in either group and was able to demonstrate stimulation of oxidative metabolism in white blood cells through carnitine uptake (Waldner et al 2006). Increased carnitine intake may be required with long term therapy — potentially beneficial interaction only under professional supervision.

Carboplatin

Treatment with carboplatin appears to result in marked urinary losses of L-carnitine and acetyl-L-carnitine, most likely due to inhibition of carnitine reabsorption in the kidney (Mancinelli et al 2007).

Cisplatin

Research into the use of L-carnitine 4 g/day for 7 days showed a reduction in fatigue resulting from treatment with cisplatin (Graziano et al 2002) — beneficial interaction is possible under professional supervision.

HIV drugs (zidovudine)

In vitro studies indicate prevention of muscle damage due to carnitine depletion (Dalakas et al 1994, Moretti et al 2002, Semino-Mora et al 1994). Patients with HIV infection undergoing highly active antiretroviral therapy can be carnitine deficient and supplementation of L-carnitine has been proposed to 'increase the number of CD4 cells and reduce lymphocyte apoptosis; improve symptoms of polyneuropathy; prevent cardiovascular damage from wasting and diarrhoea syndromes; decrease serum levels of triglycerides and TNF(alpha)' (Ilias et al 2004). Beneficial interaction is possible. Increased carnitine intake may be required with long-term therapy — use under professional supervision.

HMG CoA-reductase inhibitors (statins)

According to human trials the addition of L-carnitine (2 g/day) to simvastatin therapy (20 mg/day) appears to lower lipoprotein-a serum levels in patients with type 2 diabetes mellitus (Solfrizzi et al 2006). Beneficial interaction possible.

Interferon-alpha

Clinical trials with patients being treated with IFN-alpha for hepatitis C observed reduced fatigue when carnitine 2 g/day was co-administered (Neri et al 2003). L-Carnitine may reduce hepatic steatosis associated with IFN alpha and ribavirin treatment in patients with hepatitis C (Romano et al 2008). Increased carnitine intake may be required with long-term therapy — potentially beneficial interaction under professional supervision.

Interleukin-2 immunotherapy

Clinical trials using L-carnitine (1 g/day orally) found that it may be used successfully to prevent cardiac complications during IL-2 immunotherapy in cancer patients with clinically relevant cardiac disorders (Lissoni et al 1993). Thus a beneficial interaction is possible under professional supervision.

CONTRAINDICATIONS AND PRECAUTIONS

- Chronic liver disease — may impair metabolism or increase biosynthesis of L-carnitine (Krahenbuhl 1996).
- Seizures — may increase incidence of seizures in those with a pre-existing condition (Sigma-Tau Pharmaceuticals 1999).

PREGNANCY USE

Insufficient reliable information is available. However, animal studies have revealed no evidence of decreased fertility or harm to the fetus (Hendler & Rorvik 2001). In fact, some research suggests a role for carnitine.

Requirements for carnitine may increase during pregnancy and a small trial found a positive effect in women diagnosed with placental insufficiency taking 1 g L-carnitine twice daily (Genger et al 1988). Due to the role of L-carnitine in the synthesis of surfactant, trials have also been conducted using L-carnitine in combination with low-dose betamethasone in women with imminent premature delivery, with an improvement in respiratory distress syndrome and mortality rates (Kurz et al 1993).

PRACTICE POINTS/PATIENT COUNSELLING

- Carnitine is an amino acid that is ingested through the diet and also synthesised from lysine and methionine in the body.
- It is involved in numerous biochemical processes and is essential for energy production in the mitochondria of every cell.
- Vegetarians, and preterm infants or those on a carnitine-free formula, are at risk of deficiency. Secondary risk factors include genetic defects of metabolism, liver and renal disease, dialysis, certain medicines and hypopituitarism.
- L-Carnitine 2 g/day for 3 months has been shown to improve exercise tolerance and recovery, especially in people with cardiovascular disorders such as chronic stable angina and cardiac insufficiency. Preliminary evidence also suggests a possible role in hyperthyroidism, male infertility and peripheral vascular diseases such as intermittent claudication.
- Carnitine supplements are also used to promote weight loss and as an ergogenic aid, although large controlled studies are unavailable to assess their effectiveness.

PATIENTS' FAQs

What will this supplement do for me?

L-Carnitine supplements improve clinical outcomes in people with cardiovascular disorders by reducing the frequency of angina attacks, and improving outcomes after heart attack, cardiogenic shock and in cardiomyopathy. It may also reduce symptoms in hyperthyroidism, increase male fertility, increase walking distance in people with peripheral vascular disease and reduce the side-effects of some medicines.

When will it start to work?

People with cardiovascular disorders such as chronic stable angina and cardiac insufficiency should experience benefits within 1–3 months.

Are there any safety issues?

Carnitine is well tolerated, but people with chronic liver disease or epilepsy should use it with caution.

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Celery

HISTORICAL NOTE Celery is widely used as a food. The ancient Greeks used celery to make a wine called selinites, which was served as an award at athletic games. Dioscorides described celery as an effective remedy for 'heated stomach' and breast lumps and used it as a diuretic for urinary retention and dropsy.

OTHER NAMES
Smallage, marsh parsley, wild celery

BOTANICAL NAME/FAMILY
Apium graveolens (family Umbelliferae [Apiaceae])

PLANT PART USED
Fruit (seed)

CHEMICAL COMPONENTS
Celery is high in minerals, including sodium (Murphy et al 1978), and contains furocoumarins such as psoralen and bergapten (Beier et al 1983). The major constituents of celery seed oil include pinene and D-limonene (Saleh et al 1985). Celery also contains flavonoids, such as apigenin, luteolin and isoquercitrin, and phenolic acids and alkaloids (Fisher & Painter 1996).

MAIN ACTIONS

Anti-inflammatory activity
Celery has been found to have anti-inflammatory activity, with suppression of carrageenan-induced paw oedema observed in rats (Al-Hindawi et al 1989, Ziyan et al 2007). Several constituents show anti-inflammatory activity, such as apigenin, eugenol, ferulic acid, luteolin and bergapten (Duke 2003); and also apiin (Mencherini et al 2007). Studies in rats suggest that some celery seed extracts are highly effective in suppressing experimental arthritis without exhibiting any gastrotoxicity (Whitehouse et al 1999). Further in vivo studies suggest that celery seed extracts were gastroprotective for NSAID gastropathy and that this effect is mediated through non-prostaglandin mechanisms (Whitehouse et al 2001). Luteolin may also be useful for mitigating neuroinflammation (Jang et al 2008).

Cholagogue
Aqueous celery extract has also been found to increase bile acid excretion and lower total serum cholesterol levels in genetically hypercholesterolaemic rats (Tsi & Tan 2000).

Chemoprotective
Human in vivo trials imply that apiaceous vegetable intake may be chemopreventive by inhibiting cytochrome P450-mediated carcinogen activation (Peterson et al 2006). Based on in vivo studies in mice, it has been suggested that the phthalide components of celery may be effective chemoprotective agents (Zheng et al 1993). Other studies show that celery consumption, in particular due to its flavones luteolin and apigenin (Lim do et al 2007, Meeran 2008), has been linked to a reduced risk of developing colon cancer (Slattery et al 2000), stomach cancer (Haenszel et al 1976), liver cancer (Sultana et al 2005) and lung cancer (Galeone et al 2007).

Antioxidant
There are a number of studies providing evidence of the anti-oxidative effects of some constituents in celery (Popovic et al 2006, Yeh & Yen 2005, Zidorn et al 2005).

Lipid lowering activity
One study of vegetables, including celery, showed that cooking enhanced the amount of phytosterols which are known to decrease plasma cholesterol, mainly the atherogenic LDL cholesterol (Kaloustian et al 2008). In vivo trials of aqueous celery extract on rats showed a significant reduction in total serum cholesterol (Tsi 1995, 1996).

OTHER ACTIONS
Celery is said to have antirheumatic, carminative, antispasmodic, diuretic, antihypertensive and urinary antiseptic activity. Celery extracts have also been found to have significant activity as a mosquito repellent (Pitasawat et al 2007, Tuetun et al 2004, 2005, 2008). Research has shown that the flavones and coumarins, as well as the nutritional compounds, of vegetables including celery, have immunomodulatory functions (Cherng et al 2008). Some antimicrobial activity is also reported from in vitro studies of the essential oil component (Misic et al 2008), while other studies show celery extracts to be ineffective against gram-negative bacteria (Watt et al 2007). In vitro tests reveal the flavone apigenin has multiple effects on osteoblasts, suggesting that it could prevent bone loss in vivo (Bandyopadhyay et al 2006) and be a useful pharmacological tool for the treatment of osteoporosis (Choi 2007).

CLINICAL USE
Celery has not been significantly investigated under clinical trial conditions, so evidence is mainly derived from in vitro and animal studies and is largely speculative.

Osteoarthritis
Evidence of anti-inflammatory activity in experimental models provides a theoretical basis for its use; however, controlled trials are not available to determine effectiveness.

A small uncontrolled trial of 15 patients with chronic arthritis found that treatment with celery seed extract significantly reduced pain symptoms after 3 weeks (Bone 2003).

Urinary tract infection
Celery is used in combination with other herbal medicines for the treatment of this condition. Although it is not certain that the herb has antibacterial activity against microorganisms implicated in urinary tract infection, it is used for its diuretic effect.

OTHER USES

Traditional
Celery has been traditionally used as a diuretic, to improve appetite and digestion, and as a treatment for nervousness and hysteria. The British Herbal Pharmacopoeia gives the specific indication of celery for rheumatoid arthritis and depression (Fisher & Painter 1996).

Oriental medicine uses the seeds to treat headaches and as a digestive aid and emmenagogue.

In Trinidad and Tobago, celery is used as a heart tonic and for low blood pressure (Lans 2006); while in some parts of Indonesia it is one of a number of kitchen plants used in saunas for post-partum recuperation (Zumsteg & Weckerle 2007).

Animal studies on isolated constituents from celery have been found to be valuable in the treatment of acute ischaemic stroke via multiple mechanisms, such as strong anti-oedema activity (Deng 1997) as well as anti-oxidation, anti-apoptosis and anti-inflammatory actions (Chang 2003). Animal studies also demonstrate that the phthalide components improve cognitive impairment induced by chronic cerebral hypoperfusion, indicating its therapeutic potential for the treatment of dementia caused by decreased cerebral blood flow (Peng 2007).

DOSAGE RANGE
- Fluid extract (1:2): 4.5–8.5 mL/day in divided doses.
- Decoction of dried fruit: 0.5–2 g three times daily.

TOXICITY/ADVERSE REACTIONS
Celery can cause food allergy (Luttkopf et al 2000), with cross-reactivity to a number of other foods (Moneret-Vautrin et al 2002, Vieths et al 2002). Topical exposure to celery may cause contact dermatitis, angio-oedema and urticaria (Kauppinen et al 1980). Photodermatitis has been recorded with occupational exposure (Seligman et al 1987) and celery has been suggested to cause ocular phototoxicity (Fraunfelder 2004).

SIGNIFICANT INTERACTIONS
Controlled studies are not available, so interactions are based on evidence of activity and are largely theoretical and speculative.

NSAIDs
Celery seed extract may reduce gastrointestinal symptoms associated with NSAIDs — beneficial interaction possible.

Pentobarbital
Celery juice has been found to prolong the action of pentobarbital in rats (Jakovljevic et al 2002)— use with caution.

Warfarin
Celery contains naturally occurring coumarins, which may theoretically exert anticoagulant effects; however, interaction is unlikely (Heck et al 2000, Myers 2002) — observe with high-dose extracts.

Thyroxine
Celery seed might decrease the effects of levothyroxine replacement therapy according to one case report — observe patient.

Sodium valproate
In animal studies celery was found to have a protective effect against sodium valproate's well established toxicity to the testes and sperm production (Hamza & Amin 2007).

Psoralen–UVA (PUVA) therapy
Although celery has been found to contain psoralens, celery extract does not seem to be photosensitising, even after ingestion of large amounts; however, it may increase the risk of phototoxicity with concurrent PUVA therapy (Gral et al 1993) — use with caution.

CONTRAINDICATIONS AND PRECAUTIONS
Usual dietary intakes are likely to be safe.

PREGNANCY USE
Likely to be safe when consumed in dietary amounts; however, safety is not known when used in larger quantities.

PRACTICE POINTS/PATIENT COUNSELLING
- Celery has been traditionally used as a diuretic. It is used to treat osteoarthritis and demonstrates anti-inflammatory activity in experimental models. Celery is likely to be safe when used in quantities commonly used in foods; however, there is the possibility for allergy and contact sensitivity.
- It is prudent to avoid using celery seed essential oil in amounts greater than those ingested when used as a food.

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Chamomile

HISTORICAL NOTE Chamomiles have been used as medicines since antiquity and traditionally grouped in botanical texts under the same general heading. They were probably used interchangeably. Roman chamomile was reportedly used to embalm the Egyptian Pharaoh, Ramses II, and is thought to have been introduced into Britain by the Romans during their conquests. The Anglo-Saxons used chamomile, presumably the Roman chamomile, as one of their nine sacred herbs. Culpeper lists numerous ailments for which chamomile was used, such as jaundice, fevers, kidney stones, colic, retention of urine and inflammation of the bowel (Culpeper 1995). It was also widely used to treat common conditions in children, including colic in infants, teething pains and fever (Grieve 1976). It is used in the treatment of gout and to reduce the severity of sciatic pain, either taken internally or applied as a poultice externally (Culpeper 1995). Today, chamomile tea is one of the most popular herbal teas in Australia and New Zealand, and extracts are also used in cosmetics, as bath preparations, in hair dye for blonde hair, shampoos, mouthwashes and preparations to prevent sunburn (Foster & Leung 1996).

COMMON NAME

German chamomile

OTHER NAMES

Wild chamomile, single chamomile, Hungarian chamomile, pin heads matricaria, blue chamomile, Flos chamomillae vulgaris (Lat)

BOTANICAL NAME/FAMILY

Chamomilla recutita (L.) (family Asteraceae [Compositae])

There has been considerable confusion over botanical classification since the plant formerly known as *Matricaria recutita* L. was added to the genus *Chamomilla* in 1974. *Matricaria chamomilla* L. is also used.

PLANT PARTS USED

Flower heads, gathered in summer when they are dry, and carefully dried at low temperatures. Essential oil extracted by steam distillation of the flower heads.

CHEMICAL COMPONENTS

- Essential oil (see below) 0.24–1.9%.
- Flavonoids (including flavonols and methoxylated flavones), apigenin (other flavonols are partially hydrolysed to apigenin leading to concentrations of up to 8%), apigetrin (apigenin-7-D-glucoside), apigenin-7-acetylglucoside, apiin (apigenin-7-apiosylglucoside), rutin (quercetin-3-rutinoside), luteolin, quercimeritrin (quercetin-7-D-glucoside), quercetin and isorhamnetin.
- Coumarins — umbelliferone (7-hydroxycoumarin) and herniarin (methyl ether of umbelliferone).
- Proazulenes (sesquiterpene lactones), including matricin, matricarin and desacetylmatricarin.
- Plant acids (acidic mucilage), fatty acids, polysaccharide, choline, amino acids.

Essential oil

Chamomile extract produced by a cold extraction process is yellow; steam distillation produces the blue essential oil. This is derived from matricin, also known as proazulene or prochamazulene, a precursor of chamazulene.

Chamazulene (1–15%), farnesene, alpha-bisabolol and bisabolol oxides A and B (up to 50% of the essential oil; proportions vary depending on the chemotype), bisabolone oxide, chamazulene (from matricin on distillation), matricin, chamaviolin, spathulenol and *cis*- and *trans*-enyne dicyclo ethers (spiroether, polyacetylenes).

German chamomile has four chemotypes (variations of the plant product according to chemical composition). These relate to slight variations in the bisabolol oxide content of the essential oil (Gasic et al 1986). Chemotypes, which contain highest levels of alpha-bisabolol (known as C and D chemotypes), should be sourced when an essential oil is required for antiphlogistic or spasmolytic properties.

Clinical note — The difference between German and Roman chamomile

Chamomilla recutita is widely distributed in wastelands and in the neglected fields of Europe, particularly in Croatia and Hungary. Selected varieties are cultivated (Bruneton 1995). Many plants are referred to as chamomile or have the word 'chamomile' as part of their common name. Of the large number of species of chamomile growing in Europe, North Africa and the temperate region of Asia, five grow wild in the United Kingdom and Europe. Wild varieties are German chamomile (*C. recutita*), Roman chamomile (*C. nobile* (L.)), foetid or stinking mayweed (*Anthemis cotula*), corn chamomile (*Anthemis arvensis*), and yellow chamomile (Grieve 1976).

Roman chamomile, or *Chamaemelum nobile* (L.) (*Anthemis nobile* L.) is the 'chamomile' often referred to in English herbals. It has similar uses to the German chamomile, such as an aromatic bitter for digestive conditions, antispasmodic agent, mild sedative, and topically for its anti-inflammatory and mild analgesic properties.

MAIN ACTIONS

Anti-inflammatory

Chamomile extract and various isolated constituents within chamomile have demonstrated anti-inflammatory activity in a variety of tests.

Chamomile extract showed anti-inflammatory effects when applied topically in animal models

of inflammation (Al-Hindawi et al 1989, Plevova 1999, Shipochliev et al 1981). In a comparative trial, hydro-alcoholic extracts of chamomile produced anti-inflammatory actions when applied topically in the croton ear test in the mouse. The hydro-alcoholic extract reduced oedema in a dose-dependent manner and was equivalent in effectiveness to benzydamine at twice the usual clinical dose, but hydrocortisone was found to be the most effective treatment (Tubaro et al 1984).

Another comparative study investigated the anti-inflammatory effects of an extract prepared from dried flowers, an extract based on fresh flowers, and the volatile oil, in croton oil-induced dermatitis of mouse ear. The activity of fresh chamomile equaled the activity of the reference drug (benzydamine).

The anti-inflammatory activity of the herb appears to be due to several different constituents, chiefly apigenin, matricin, chamazulene and alpha-bisabolol, although others may also exist.

The previous study determined that apigenin exerts the strongest anti-inflammatory action, which is 10 times greater than matricin, which is 10 times greater than chamazulene (Della Loggia et al 1990). Another study evaluated the effects of apigenin on the lipopolysaccharide-induced proinflammatory cytokines IL6 and TNF-alpha in vitro and in vivo (Smolinski & Pestka 2003). Apigenin reduced IL6, but not TNF-alpha in vitro. Pretreatment with the flavone (50 mg/kg) reduced IL6 by 35% and TNF-alpha by 33% in vivo as compared with control animals. Alpha-bisabolol has demonstrated anti-inflammatory and analgesic effects in a number of experimental inflammatory models: rat paw oedema, adjuvant arthritis of the rat, ultraviolet erythema of the guinea pig, and yeast fever of the rat (Jakovlev et al 1979). Sodium azulene sulphate, a water-soluble derivative of azulene, has demonstrated the ability to reduce plasma exudation in a recently developed model of capsaicin-induced pharyngitis (Sakai et al 2005).

Most studies have investigated the effects of topically applied chamomile or isolated constituents; however, one study using the carrageenan inflammation test on rat paws showed that orally administered matricin produces anti-inflammatory activity that was greater than chamazulene and almost as effective as (-)-alpha-bisabolol (Jakovlev et al 1979, Shipochliev 1981a).

Chamazulene has been found to inhibit leukotriene B4 formation and blocks chemical peroxidation of arachidonic acid (Safayhi et al 1994).

Antipuritic

An ethyl acetate extract and essential oil of chamomile have both shown antipuritic activity after a single dose in vivo (Kobayashi et al 2005). Additionally, the antipuritic effects of the antihistamine H1 antagonists, oxatomide and fexofenadine, were significantly increased by the ethyl acetate extract.

Antispasmodic

Chamomile extract and several constituents demonstrate a dose-dependent antispasmodic effect in vitro. The major activity is related to bisabolol, spiroethers and apigenin. (-)-alpha-bisabolol has an effect equal to papaverine; apigenin was the most potent flavonoid, being significantly more potent than papaverine. The extract of chamomile also has a good spasmolytic activity (Achterrath-Tuckermann et al 1980).

Sedative

Shinomiya et al found that 300 mg/kg of chamomile extract significantly decreased sleep latency in a sleep-disturbed rat model, demonstrating benzodiazepine-like activity (Shinomiya et al 2005). Extracts of chamomile showed sedative activity on the mouse CNS (Della Loggia et al 1981), and extracts of chamomile, as well as isolated apigenin, have been shown to bind to benzodiazepine receptors in vitro. Apigenin showed antianxiety and sedative activity with intraperitoneal injection in mice (Viola et al 1995).

Ovariectomised rats given inhalations of chamomile oil showed decreased levels of stress-induced ACTH levels compared with controls; the experiment suggested an activity similar to benzodiazepine agonists (Yamada et al 1996).

Antimicrobial

According to in vitro studies, the essential oil has bactericidal and fungicidal activities against gram-positive bacteria (*Bacillus subtilis*, *Staphylococcus aureus*) and *Candida albicans* in concentrations above 0.05% v/v, but has no effect against the gram-negative bacteria *Escherichia coli*, *Pseudomonas aeruginosa* (Aggag & Yousef 1972) and *Salmonella typhimurium* (Gomes-Carneiro et al 2005). In contrast, extracts of chamomile have demonstrated antimicrobial activity against *E. coli* (Ceska et al 1992). The growth of *S. aureus*, *Streptococcus mutans* and group B streptococcus was inhibited by chamomile extract at concentrations of 10 mg/mL (Cinco et al 1983), whilst a very low concentration of the essential oil (0.0075% v/v) effectively inhibited *Helicobacter pylori* (Weseler et al 2005).

Extracts of chamomile may also inhibit *Herpes simplex* virus (HSV). One study found that a semi-purified extract of chamomile was effective in inhibiting HSV in vitro (Suganda et al 1983), whilst another found the essential oil to have significant virucidal activity against HSV type 2 (Koch et al 2008). In vitro tests using apigenin have identified inhibitory activity against HIV activation, possibly by affecting viral transcription (Critchfield et al 1997, Trovato et al 2000).

Anti-ulcer

Chamomile extract protected rats from developing experimentally induced ulcers. Bisabolol (and extracts of chamomile) prevented the formation of ulcers in experimental animals exposed to indomethacin (NSAID) stress, and alcohol; and reduced the healing time of ulcers induced by chemical stress (acetic acid) or by heat coagulation.

Wound healing

Alpha-bisabolol promotes granulation and tissue regeneration in burns and ulcers, and protects

against their formation (Szelenyi et al 1979). Oral administration of an aqueous extract of chamomile (120 mg/kg/day) significantly decreased healing time for excision, incision and dead space wounds in vivo (Nayak et al 2007). Another study evaluated the topical application of chamomile in vivo and found that it significantly improved healing time for second degree burns (Jarrahi 2008).

OTHER ACTIONS

Immune enhancement

Chamomile extract increased T-lymphocyte rosette formation in vitro in blood samples taken from ear, nose and throat patients with immunodeficiency (Kliachko et al 1994). The polysaccharides (heteroglycans) showed significant immunostimulating activities according to the granulocytes and carbon clearance tests (Wagner et al 1985).

Antioxidant

Chamazulene is a potent antioxidant. It inhibits lipid peroxidation in vitro (Goeters et al 2001) in a dose–concentration- and time-dependent manner (Rekka et al 1996).

Choleretic

Chamomile increases the production of bile by the liver (Pasechnik 1966).

Drug dependence

Chamomile extract was shown to inhibit the development of morphine dependence and expression of abstinence syndrome in rats. Chamomile reduced frequencies of behaviours associated with withdrawal (paw tremor, rearing, teeth chattering, body shakes, ptosis, diarrhoea and urination) and weight loss (Gomaa et al 2003).

Anticarcinogenic

Apigenin inhibits carcinogenesis in a number of in vitro and animal studies (Aguilera et al 2000, Ali-Shtayeh et al 2000, Birt et al 1986, 1997, Lepley & Pelling 1997, Lepley et al 1996, Panes et al 1996, Patel et al 2007, Srivastava & Gupta 2007, Umezu 1999, Wei et al 1990).

Uterine effects

Water extracts of chamomile increased uterine tonus in isolated rabbit and guinea pig uterine horn (Shipochliev 1981b).

Pigmentation

Chamomile extract has been found to decrease UV-induced pigmentation as well as the hyperpigmentation found in lentigo senilis (aged or liver spots). Endothelin-1 is a cytokine responsible for stimulating melanocyte function leading to hyperpigmentation. Chamomile has been shown to interrupt the endothelin-1-induced signalling, thereby reducing the ability of melanocytes to proliferate and to synthesise melanin (Ichihashi et al 1999).

CLINICAL USE

Chamomile is most widely taken as a tea, often after meals or as an alternative to caffeine-containing beverages. In clinical practice, the oral dose form most often used is a concentrated extract, in order to produce stronger therapeutic effects. It is also used as a topical treatment in some indications.

Skin conditions

Chamomile is used topically for a variety of dermatological conditions. The most tested topical product is commercially known as Kamillosan.

Wound healing

According to a double-blind trial, external application of a chamomile extract improves wound healing. In the study, chamomile extract significantly decreased weeping and improved wound healing after dermabrasion of tattoos (Glowania et al 1987).

Eczema

In one comparative study, 161 patients with eczema on the arms and lower legs were treated with 0.25% hydrocortisone, 5% bufexamac (NSAID), 0.75% fluocortin (glucocorticoid) or a chamomile cream commercially known as Kamillosan. The chamomile cream was as effective as hydrocortisone and was superior to the other two treatments (Aertgeerts et al 1985). (Kamillosan is reportedly made from a high bisabolol-containing chemotype of chamomile.)

Dermatitis

A study involving experimentally induced toxic dermatitis found that chamomile ointment (Kamillosan) produced a more soothing effect on human skin than a chamomile ointment base or hydrocortisone ointment 0.1% (Nissen et al 1988). (Note: the hydrocortisone cream used in this study was quite weak compared with the usual strength of 0.5–2.5%.)

Chamomile cream helped to protect against skin radiation damage in breast cancer patients receiving radiation (Maiche et al 1991). Chamomile cream (Kamillosan) has been shown to be slightly less effective than 0.25% hydrocortisone, but superior to fluocortin butyl ester and 5% bufexamac in relieving inflammation associated with dermatoses (Aertgeerts 1984, Aertgeerts et al 1985).

Commission E approves the external use of chamomile for inflammation of the skin and mucous membranes, as well as for bacterial skin diseases, including those of the oral cavity and gums (Blumenthal et al 2000).

Sedation

Both oral dose forms and the essential oil of chamomile are used for this indication.

A placebo-controlled study involving 22 volunteers found that inhalation of chamomile oil produced sedative effects and improved mood (Roberts & Williams 1992). Chamomile tea (two teabags in 175 mL of hot water) given to 12 patients during cardiac catheterisation induced a deep sleep in

10 patients, even though the procedure usually causes pain and anxiety (Gould et al 1973).

Gastrointestinal conditions

Chamomile is widely used to relieve stomach cramping, dyspepsia and flatulence. The herb's antispasmodic and relaxant effects provide a theoretical basis for its use in these conditions.

In an open, multicentre study, 104 patients with gastrointestinal complaints, including gastritis, flatulence and minor spasms of the intestines, were treated for 6 weeks with 5 mL/day of an oral chamomile preparation (standardised to contain 50 mg alpha-bisabolol and 150–300 mg apigenin-7-glucoside per 100 g). By self-evaluation, all patients improved with 44.2% becoming symptom free (Stiegelmeyer 1978).

Diarrhoea in children

In Europe, chamomile is widely used to treat a variety of paediatric complaints.

A prospective, double-blind, randomised trial was used to document the efficacy of a preparation containing chamomile extract and pectin (Diarrhoesan) in children aged 6 months–5.5 years with uncomplicated diarrhoea. The chamomile preparation reduced the duration and severity significantly faster than placebo (de la Motte et al 1997). A larger multicenter, double-blind, RCT involving 255 patients was designed to further evaluate the apple pectin and chamomile preparation for acute diarrhoea in children aged between 6 months and 6 years (Becker et al 2006). Stool frequency was significantly reduced in the treatment group as compared to placebo. Commission E approves chamomile for gastrointestinal spasms and inflammatory diseases of the gastrointestinal tract.

Antibacterial preparations

A phase III, double-blind, placebo-controlled clinical trial of 164 patients assessed the efficacy of chamomile mouthwash in preventing 5-fluorouracil-induced stomatitis and found no difference between chamomile and placebo (Fidler et al 1996).

OTHER USES

The British Herbal Pharmacopoeia (1983) recommends chamomile for flatulent nervous dyspepsia, travel sickness, nasal catarrh, nervous diarrhoea and restlessness. Externally, chamomile is recommended for haemorrhoids, mastitis and leg ulcers. The specific indication is for gastrointestinal disturbance with nervous irritability in children and for teething and colic in infants.

Commission E approves the use of inhalations for inflammation and irritation of the respiratory tract and baths and irrigations for anogenital inflammation (Blumenthal et al 2000).

Oral mucositis/recurrent aphthous stomatitis

Methotrexate-induced oral mucositis in a 76-year-old woman was successfully treated by chamomile mouthwash in a recently reported case study (Mazokopakis et al 2005). The mouthwash consisted of 8 g of flower heads steeped in 1000 mL of boiling water for 15 min and then used as a gargle four times daily.

The fluid extract of chamomile appears to exert an analgesic effect on the oral mucosa. Thirty-four patients applied chamomile extract directly to their mouth ulcer(s) and then repeated this process at intervals of 5, 10 and 15 min in an unblinded, uncontrolled clinical trial. The effect was rated as excellent by 82% and good by 18% of participants using an Analogical Visual Scale (Ramos-e-Silva et al 2006).

Preventing postoperative sore throat

Chamomile extract spray administered before intubation was not able to prevent postoperative sore throat and hoarseness compared with saline spray in a randomised, double-blind study (Chan et al 2003).

Haemorrhagic cystitis

Chamomile extract decreased the symptoms of haemorrhagic cystitis. Thirty-two patients were randomly assigned to receive either the antibiotic cotrimoxazole (trimethoprim/sulfamethoxazole) alone or with a chamomile extract administered on day one as a bladder instillation, followed by daily hipbath use. Symptoms were evaluated after 10 days and indicated that the chamomile group experienced more rapid alleviation of symptoms than the group treated with only cotrimoxazole. The product used was Kamillenextrakt, an ethanolic extract of chamomile flowers (Barsom et al 1993).

DOSAGE RANGE

Internal use

- German chamomile is used either as a tea made from the dried flower heads, or as an extract.
- Dried flower heads: 2–8 g three times daily by infusion.
- Fluid extract (1:2): 3–6 mL/day.
- Tincture (1:5): 3–10 mL three times daily.
- The quality of chamomile varies greatly. For maximum efficacy, use high-grade chamomile (high in alpha-bisabolol). Standardised extracts are usually standardised to either bisabolol or apigenin.

External use

- The dried flowers can also be made into a poultice with the addition of hot water and applied directly to the skin, or the tea can be used to bathe inflamed skin and eyes.
- Essential oil (external use): Five drops per 100 mL of oil, or per 100 g of cream or ointment.
- In baths and water for compresses, the dose should not exceed 10 drops.
- Inhalation: Five drops of essential oil in 1 L hot water.

ADVERSE REACTIONS

Allergic reactions

Occasional rare cases of allergic skin reactions have been reported. However, a bibliographic review of 50 reports of 'chamomile' sensitivity revealed that in only five papers was the botanical identification

of the plant material correlated with *Chamomilla recutita*. In the majority of other instances, the effects were caused by species of the genus *Anthemis*, frequently also called chamomile. Experimental studies on pigs using a rigorous testing technique proved that *C. recutita* possesses low sensitising capacity. The suspected allergen is the sesquiterpene lactone, anthecotulide, found in *Anthemis cotula* L. (stinking mayweed), which only occurs in trace amounts in the bisabolol oxide B-chemotype of genuine chamomile (Hausen et al 1984). Allergic conjunctivitis has been reported with the use of chamomile tea eyewashes, and the pollens contained in the teas have been identified as the allergens responsible. The reaction occurred after first exposure and was thought to be due to cross-reactivity to *Artemesia* pollen (Subiza et al 1989). Pollens are not likely to be present or active in aqueous alcohol extracts of chamomile.

German chamomile is thought to be less allergenic than Roman chamomile, but any variety of chamomile can potentially cause allergic reactions. An enema made from German chamomile (Kamillosan) given during labour to a 35-year-old woman with no history of atopy resulted in life-threatening anaphylaxis and fatal asphyxia of the newborn (Jensen-Jarolim et al 1998). Chamomile enemas are not a usual form of administration.

SIGNIFICANT INTERACTIONS

Controlled studies are not available; therefore, interactions are based on evidence of activity and are largely theoretical and speculative.

Benzodiazepines

Theoretically, an additive CNS depressant and antispasmodic effect can occur with concurrent use. Observe patients taking this combination, although the combination may be clinically useful when used under supervision.

Warfarin

A case of multiple internal haemorrhage in a 70-year-old woman using topical and oral chamomile products in conjunction with warfarin has been described (Segal et al 2006). Observe.

Drugs metabolised by CYP3A4

Chamomile has been shown to inhibit cytochrome 3A4 enzymes in vitro (Budzinski et al 2000, Ganzera et al 2006, Gomes-Carneiro et al 2005). The clinical significance of this is unknown; however, drugs that are metabolised by these enzymes could theoretically be affected. Until this can be confirmed or refuted in a clinical study, observe for interactions.

NSAIDS

Chamomile extract protected test animals from experimentally induced ulcers — beneficial interaction.

CONTRAINDICATIONS AND PRECAUTIONS

Chamomile is contraindicated in hypersensitivity or known allergy to chamomile or other members of the Asteraceae family (e.g. yarrow, tansy, feverfew, daisy, ragweed).

A recent investigation found that 7.5% of the 200 samples evaluated were contaminated with *Clostridium botulinum* spores (Bianco et al 2008). This could be potentially dangerous for infants. The investigators found that the presence of these spores was significantly higher in bulk chamomile sold by weight as opposed to packaged tea ($P = 0.005$). Caution is advised when giving chamomile to children aged less than 12 months.

PREGNANCY USE

Safety has not been established scientifically; however, no teratogenic effects have been observed in vivo.

PRACTICE POINTS/PATIENT COUNSELLING

- German chamomile has demonstrated anti-inflammatory, antispasmodic, sedative and antimicrobial activity.
- It is taken orally either as a tea or tincture, used externally as a poultice, cream or ointment or inhaled as an essential oil.
- Internally, it is used to relieve flatulence, gastrointestinal spasm, dyspepsia and induce a sense of relaxation. It is also used for infants with teething pain and colic.
- Externally, chamomile preparations are used to treat dermatitis, enhance wound healing, nappy rash and soothe irritated skin. Comparative studies show that it has an anti-inflammatory effect equivalent to low-dose hydrocortisone preparations.
- There is some evidence from clinical trials to support the use of chamomile in the treatment of wounds, eczema, dermatitis, nervousness and tension, diarrhoea in children and for the symptoms of haemorrhagic cystitis (in association with antibiotic therapy).

PATIENTS' FAQs

What will this herb do for me?

Chamomile is taken to relieve stomach spasms and flatulence, to induce relaxation and promote sleep. It is also popular for children with teething pain and digestive complaints such as colic or diarrhoea. Applied externally as a cream, ointment or poultice, it is used to reduce skin irritation and inflammation.

When will it start to work?

Chamomile relieves gastrointestinal symptoms quickly, within several minutes. For more chronic problems, it may need to be used long term.

Are there any safety issues?

Chamomile is considered a very safe herb. While there have been reports of allergic reactions, the majority have been due to adulteration with other herbs. Chamomile tea is more likely to cause allergic reactions than either extracts or essential oil. Chamomile should not be used by persons with hypersensitivity or known allergy to chamomile or other members of Asteraceae family (e.g. yarrow, tansy, feverfew, wormwood).

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Chaste tree

HISTORICAL NOTE Chaste tree fruits and leaves were a popular remedy in ancient Greece and Rome to promote celibacy. Leaves of the chaste tree were worn by vestal virgins in ancient Rome as a symbol of chastity. In the 17th century it was written that the chaste tree is a 'remedy for such as would willingly live chaste' (Gerard 1975). The dried fruits of the chaste tree have a peppery taste and smell and were used in place of pepper in monasteries to 'check violent sexual desires', hence one of its common names, Monk's Pepper. The berries have also been used to reduce fever and headaches, stimulate perspiration and dispel wind. However, since ancient times the chaste tree has primarily been used for a variety of gynaecological purposes, primarily menstrual abnormalities, mastalgia, to aid in expulsion of the placenta after birth, to facilitate lactation, and to promote menstruation. A commercial preparation of chaste tree has been available in Germany for over 50 years and it is still commonly used for menstrual irregularities.

OTHER NAMES

Vitex, agnus castus, chasteberry, monk's pepper, gattilier, hemp tree, Keusch-Lamm-Fruechte, wild pepper.

BOTANICAL NAME/FAMILY

Vitex agnus-castus (family Labiatae)

PLANT PART USED

Dried, ripened or fresh ripe fruits (berries)

CHEMICAL COMPONENTS

Vitex agnus-castus contains many different chemical constituents, including luteolin-like flavonoids (casticin, orientin, isovitexin), iridoid glycosides, aucubin, eurostoside, agnuside, essential fatty acids and the essential oils cineole, limonene and sabinene.

MAIN ACTIONS

Vitex displays multiple mechanisms of action identified through in vitro and experimental model research.

One major area of activity is the pituitary–hypothalamic axis.

Decreases prolactin release

The most thoroughly studied mechanism for vitex is its interaction with dopamine receptors in the anterior pituitary. Several studies have indicated that vitex acts on dopamine D_2 receptors and decreases prolactin levels (Berger et al 2000, Halaska et al 1998, Jarry

et al 1994, Meier & Hoberg 1999, Meier et al 2000, Milewicz et al 1993, Sliutz et al 1993, Wuttke et al 2003). It is likely that this mechanism is responsible for the symptom-relieving effects seen with vitex in mastodynia and hyperprolactinaemia (Meier & Hoberg 1999, Milewicz et al 1993, Splitt et al 1997) and provides some rationale for its use by herbalists in disorders complicated by hyperprolactinaemia, such as amenorrhoea, mastalgia or polycystic ovarian syndrome.

Results from one study involving healthy males propose that this effect is dose-dependent, as lower doses (120 mg) were found to increase secretion and higher doses (204–480 mg) were found to decrease secretion (Merz et al 1996).

A study using the vitex extract BNO 1095 (70% ethanol, 30% H_2O extract, Bionorica AG, Neumarkt, Germany) identified that the major dopaminergic compounds are the clerodadienols, which act as potent inhibitors of prolactin release; however, other active compounds of lesser activity were also identified (Wuttke et al 2003). Dopaminergic bicyclic diterpenes have also been isolated that inhibit cAMP formation and prolactin release in rat pituitary cell cultures (Jarry et al 2006).

Oestrogen receptor binding

Vitex contains oestrogenic compounds, the flavonoids penduletin and apigenin. Vitex extract showed significant competitive binding to oestrogen receptors alpha and beta in vitro (Liu et al 2001, Jarry et al 2003, Wuttke et al 2003).

Increases progesterone levels

In vitro research has found that vitex stimulates progesterone receptor expression (Liu et al 2001). A randomised controlled trial of women with hyperprolactinaemia showed that vitex extract (20 mg daily) normalises progesterone levels after 3 months' treatment (Milewicz et al 1993).

Opioid receptors

A recently published study reported that a methanol extract of vitex had affinity to the μ-opiate receptor (Webster et al 2006). Of note, this receptor is the primary action site for beta-endorphin in vivo, a peptide which assists in regulating the menstrual cycle through inhibition of the hypothalamus–pituitary–adrenal axis.

> ***Clinical note — The opiate system and PMS***
> The opiate system consists of mu, delta and kappa opiate receptors and endogenous opiate peptides such as beta-endorphin (Webster et al 2006). The opiate system plays an essential role in regulating tonic pain perception, mood, appetite, and other functions. PMS is characterised by a reduction of opiate activity and the severity of symptoms such as anxiety, food cravings, and physical discomfort is inversely proportional to the amount of decline in beta-endorphin levels in the luteal phase. Based on recent research, the symptom-relieving effects of vitex in PMS may be due to direct activation of analgesic and mood regulatory pathways via opiate receptor activation and/or reversal of the loss of opiate inhibition in the luteal phase.

Cytotoxic activity

Cytotoxic activity has been reported for an ethanolic extract of the dried ripe fruit of vitex against various human cancer cell lines (Ohyama et al 2003, 2005, Weisskopf et al 2005). The extract increased intracellular oxidative stress and mitochondrial damage leading to apoptosis. In vitro studies demonstrate that vitex extract inhibits the proliferation of human prostate epithelial cell lines via apoptosis (Weisskopf et al 2005).

OTHER ACTIONS

Conflicting results have been obtained in studies with regard to the effect on follicle-stimulating hormone (FSH) and luteinising hormone (LH) levels. One clinical study found that vitex extract did not alter FSH or LH levels, whereas another showed that it increased LH release (Lauritzen et al 1997, Milewicz et al 1993). Inconsistent results may be due to variations in chemical constituent levels present in the different test herbal products.

CLINICAL USE

Although double-blind studies have recently been conducted with chasteberry, uncontrolled trials go back to the 1940s when a product known as Agnolyt was tested. The product was developed and patented by Dr Gerhard Madaus in Germany and contained *Vitex agnus-castus*. Several different vitex products have been investigated to date including: Agnolyt (standardised to 3.5–4.2 mg of dried chasteberry extract), *Vitex agnus-castus* L. extract Ze 440 (each 20 mg tablet standardised for casticin and agnuside), Femicur (contains 1.6–3.0 mg of dried extract per capsule) and Mastodynon (53% v/v ethanol), a homeopathic preparation. The BNO 1095 extract contains 4.0 mg of dried ethanolic (70%) extract of vitex (corresponding to 40 mg of herbal drug) and is found in Agnucaston®/Cyclodynon® (manufacturer: Bionorica AG, Neumarkt, Germany).

Premenstrual syndrome

Vitex is an effective and well-tolerated treatment for mild, moderate and severe premenstrual syndrome (PMS) according to clinical trials (Atmaca et al 2003, Berger et al 2000, Dittmar 1992, Lauritzen et al 1997, Loch et al 2000, Schellenberg 2001, He et al 2009). According to these studies, the PMS symptoms that respond best to treatment are breast tenderness, irritability, depressed mood, anger, mood changes, headache and constipation. The most studied extract investigated in PMS is Ze440 and, more recently, BNO 1095 extract (see *Clinical note,* p 307).

A multicentre, randomised, controlled, double-blind study investigating the effects of vitex (Ze440) for PMS involved 170 women and was published in the British Medical Journal (Schellenberg 2001). Of the group, 13% were also taking oral contraceptive pills (OCP). Treatment with a 20 mg tablet of dry extract of chasteberry taken daily resulted in a significant improvement of PMS symptoms,

particularly headache, breast fullness, irritability, anger and mood changes. Over 50% of women in the active treatment group achieved at least a 50% reduction in symptoms. Similar results were obtained in a 2006 prospective, open, non-comparative study of 121 women with moderate to severe PMS who took vitex (BNO 1095) over three menstrual cycles. Assessment using the validated PMS Diary (PMSD) and the PMTS score showed that the severity of PMS symptoms consistently decreased during treatment (Prilepskaya et al 2006).

The results were confirmed once again in a 2009 multicentre randomised, placebo-controlled study completed in China, testing vitex (BNO 1095) extract over three menstrual cycles in 202 women with moderate to severe PMS. Women taking hormonal contraceptives, antidepressants, selective serotonin reuptake inhibitors (SSRIs) or prolactin inhibitors during last 6 months were not included. Treatment with vitex extract BNO 1095 produced a significantly greater decrease in the total score for PMSD in the luteal phase and PMTS self-assessment compared to placebo after two menstrual cycles, with the differences between placebo and active treatment groups becoming even more significant after 3 months treatment. This further supports the use of vitex in PMS and indicates that full benefits require at least three menstrual cycles to become established (He et al 2009).

Previously, a number of open studies had generally produced positive results for Vitex as a symptomatic treatment in PMS. One multicentre, open-label study showed that daily treatment with a 20 mg tablet of vitex (Ze440) over three menstrual cycles significantly reduced the Moor menstrual distress self-assessment questionnaire (MMDQ) with 46% of women experiencing a 50% reduction in the MMDQ. Treatment also reduced the duration of PMS symptoms from 7.5 days to 6 days and was as effective for women taking OCP as for those who were not (Berger et al 2000). Once treatment was stopped, PMS symptoms gradually returned to baseline within three further cycles. The largest multicentre trial was an open study of 1634 women with PMS, which found that treatment with vitex (Femicur) for three menstrual cycles decreased the number of PMS symptoms in 93% of subjects (Loch et al 2000). Symptoms completely resolved in 40% of subjects and 94% overall rated vitex treatment as well tolerated. An early study using vitex (Agnolyt) in 1542 women with PMS reported an improvement in symptoms with an average dose of 42 drops daily taken for an average of 25 days (Dittmar 1992 as reported in Ulbricht & Basch 2005). According to Ulbricht and Basch (2005), three earlier uncontrolled studies produced inconclusive results.

Comparison to SSRI drugs

In 2003, a randomised 8-week study involving 42 women compared the effects of 20–40 mg daily of fluoxetine, a SSRI, and 20–40 mg of vitex extract and found no statistically significant difference between the groups with respect to the rate of responders (Atmaca et al 2003). More specifically, patients with premenstrual dysphoric disorder responded well to both treatments; however, fluoxetine was more effective for psychological symptoms such as depression and irritability, whereas the herbal extract was more effective for diminishing physical symptoms such as breast tenderness, cramps, food cravings and swelling. Unfortunately, the authors did not report the type of vitex extract used in the study.

Clinical note — Ze440 extract

The naming of the Ze440 extract (Premular in Australia) is derived from the name Zeller, the 135-year-old Swiss company manufacturing it, combined with a unique number ascribed during the initial studies. In order to ensure that products deliver consistent results, Ze440 is measured by both composition and consistency from batch to batch. To promote product uniformity, every batch is grown, harvested and manufactured into tablets under controlled conditions and is extracted in a standardised method that ensures consistent and high levels of the important lipophilic compound casticin and an established marker compound, the iridoid glycoside named agnuside.

Comparison to vitamin B6

Although vitamin B6 (pyroxidine) is a popular treatment for PMS symptoms, the results from a double-blind comparative study have found that vitex (Agnolyt) is as effective and possibly more so (Lauritzen et al 1997). The randomised, double-blind study of 175 women compared vitex, pyridoxine and placebo. In the study, 77% of women receiving vitex reported symptom alleviation compared with 61% with pyridoxine (200 mg/d), which was considered a small but significant difference. Additionally, physician assessments were more likely to rate treatment with vitex as 'excellent' compared with pyridoxine.

Commission E approves the use of vitex for premenstrual syndrome.

Mastalgia

Mastalgia is considered to relate to latent and increased basal prolactin levels; therefore, agents that reduce prolactin levels are anticipated to reduce symptoms. Vitex is a popular treatment for cyclical mastalgia as it interacts with dopamine D_2 receptors to reduce prolactin levels.

In two randomised, double-blind studies, vitex (Mastodynon) effectively reduced premenstrual mastalgia (Halaska et al 1998, Splitt et al 1997, Wuttke et al 2003). Subjects completed a visual analogue scale (VAS) and rated their breast pain from 0 (lowest breast pain) to 10 (extremely strong breast pain). Active treatment reduced the mastalgia score by 35–40%, an effect significantly stronger than that of placebo (25%). One of these studies also demonstrated that treatment with vitex reduced serum prolactin levels (Splitt et al 1997, as reported in Wuttke et al 2003). According to Halaska et al (1998), symptom relief was experienced after the first month of treatment

with continued improvements experienced after the second and third months.

Commission E approves the use of vitex for this indication.

Irregularities of the menstrual cycle

Vitex is used to normalise menstruation in women with shortened, lengthened or infrequent menstruation, particularly when low progesterone and luteal phase defects are suspected. In practice, vitex has also been used traditionally to treat both amenorrhoea and menorrhagia. Herbalists speculate that beneficial effects obtained in practice may be due to the herb's ability to reduce elevated prolactin levels in these conditions. This is particularly indicated where chronic stress is also present as this has an effect on the hypothalamus–pituitary axis resulting in elevated prolactin levels (Mills 2000, Trickey 1998). Whilst the use of vitex in all these indications has not yet been tested under double-blind conditions, one randomised controlled trial of women with luteal phase defect due to latent hyperprolactinaemia demonstrated that vitex extract (20 mg daily) effectively reduced prolactin levels and normalised luteal phase length and progesterone levels after treatment for 3 months (Milewicz et al 1993).

Commission E approves the use of vitex for this indication.

Menopause (in combination)

Vitex has been studied as part of several different polyherbal treatments for effectiveness in treating menopausal symptoms. The use of herbal combinations reflects real-world practice but makes it difficult to assess the value of vitex as a stand-alone treatment for this indication. To date, these studies using combination herbal therapy, including vitex, have produced mixed results.

Vitex (200 mg daily) in combination with other herbs, notably black cohosh, produced a significantly superior mean reduction in menopausal symptoms compared to placebo according to a 2007 randomised controlled study (Rotem & Kaplan 2007). The study of 50 healthy pre and postmenopausal women found herbal treatment improved menopausal symptoms gradually and after 3 months of treatment, there was a 73% decrease in hot flushes and a 69% reduction in frequency of night sweats, accompanied by a decrease in their intensity and a significant benefit in terms of sleep quality. Importantly, hot flushes ceased completely in 47% of women in the study group compared with only 19% in the placebo group. No changes were detected for vaginal epithelium or levels of relevant hormones (oestradiol, follicle-stimulating hormone), liver enzymes or thyroid-stimulating hormone in either group.

An Australian double-blind, randomised, placebo-controlled, parallel study using a combination of vitex with St John's Wort in 100 late-perimenopausal or postmenopausal women experiencing hot flushes and other menopausal symptoms failed to show significant clinical improvements in menopausal symptoms compared to placebo (van Die et al 2009).

Poor lactation

Vitex has been used since ancient times as a galactagogue to promote milk production, especially in the first 10 days after delivery.

Currently, there are no double-blind studies to confirm its efficacy; however, an early uncontrolled study provides some support for the use of vitex in lactation, finding a favourable effect on milk production in 80% of women (Noack 1943). Results from a small study of males suggest that increases in prolactin may be possible with low-dose vitex (120 mg daily) whereas higher doses (480 mg daily) result in decreased levels (Merz et al 1996).

Fertility disorders

Vitex is used in practice with other herbal medicines to enhance fertility in women with progesterone deficiency or luteal phase defects. Currently, no large studies have been published to evaluate the effectiveness of this approach; however, a double-blind, randomised, placebo-controlled study of 96 women with fertility disorders (38 with secondary amenorrhoea, 31 with luteal insufficiency and 27 with idiopathic infertility) used the vitex product Mastodynon with encouraging results (Gerhard et al 1988). Treatment of 30 drops was administered twice daily for 3 months and resulted in women with amenorrhoea or luteal insufficiency achieving pregnancy more than twice as often as the placebo group, with 15 women conceiving during the study period ($n = 7$ with amenorrhoea, $n = 4$ with idiopathic infertility, $n = 4$ with luteal insufficiency). Although promising, this study has been criticised for pooling of diverse conditions, unclear reporting of results and variable significance (Ulbricht & Basch 2005).

Acne vulgaris

An open study of 117 subjects (male and female) with different forms of acne found that after 6 weeks' treatment with a 0.2% dried extract of *vitex agnus-castus* and a topical disinfectant, 70% of cases experienced total resolution with the highest success rates reported for acne vulgaris, follicularis and excoriated acne (Amann 1975). A group that was not treated with the herb took 30–50% longer to achieve similar results. Although encouraging, it is difficult to determine the contribution of vitex treatment to these results. Until controlled studies using vitex as a stand-alone treatment are conducted, the herb's role in this condition is still uncertain.

OTHER USES

Vitex is used to aid the expulsion of the placenta after birth. It is also used to treat fibroids, normalise hormones following the use of OCP, and in cases of premature ovarian failure. Studies on rats suggest that the dopaminergic agonist action of vitex may be useful to reduce or control epileptic seizures (Saberi et al 2008).

DOSAGE RANGE

General guide

- Liquid extract (1:2): 1–2.5 mL in the morning.
- Dried fruit: 1.5–3 g in the morning.

- Dry fruit flesh (solid-dose form): 1000–1800 mg/day.
- Manufacturers have recommended vitex preparations be taken daily as a single dose upon rising, before breakfast, throughout the menstrual cycle.

According to clinical studies

- PMS
  Ze440 extract (Premular) 20 mg daily.
  Femicur 40 mg daily.
- Cyclic mastalgia
  Mastodynon 60 drops daily or 1 tablet daily.
- Menstrual irregularities
  20 mg daily (extract unknown).
- Infertility
  Mastodynon 30 drops twice daily.

ADVERSE REACTIONS

A systematic review of the herb's safety, published in 2005, analysed data from six electronic databases, postmarketing surveillance studies, spontaneous reporting schemes (including WHO), herbalist organisations and manufacturers (Daniele et al 2005). The review concluded that vitex is a safe herbal medicine and any adverse effects associated with its use tend to be mild and reversible. The most common adverse effects are: nausea, headache, gastrointestinal disturbances, menstrual disorders, acne, pruritis and erythematous rash. Additionally, no drug interactions have been reported. More recently, a 2009 placebo-controlled study of 202 women with moderate to severe PMS found no significant difference between incidence of adverse effects in the placebo- or vitex-treated groups (He et al 2009). Headache was reported as one of the more common side effects experienced by both groups which was attributed to the PMS itself and not treatment.

SIGNIFICANT INTERACTIONS

Controlled studies are not available, so interactions are based on evidence of activity and are largely theoretical and speculative.

Dopamine antagonists

An antagonistic interaction is theoretically possible — observe patients.

Oral contraceptives

There has been speculation about the effectiveness of vitex when OCP are being taken. Several clinical studies involving women taking oral contraceptives have confirmed the herb still reduces PMS symptoms and does not affect OCP.

CONTRAINDICATIONS AND PRECAUTIONS

People with tumours sensitive to oestrogen or progesterone should avoid using this herb until safety can be established.

PREGNANCY USE

Vitex is not traditionally recommended in pregnancy. In practice, some herbalists use it during the first 8 weeks of pregnancy in cases of difficult conception.

PRACTICE POINTS/PATIENT COUNSELLING

- Clinical trials support the use of vitex in mild, moderate and severe PMS. It is particularly suited to treating common PMS symptoms such as mood changes and irritability, breast tenderness, headaches and constipation. According to the available evidence, it is more effective than pyridoxine treatment and has a similar response rate to fluoxetine.
- It may also be effective in the treatment of menstrual irregularities and mastalgia.
- Vitex is also used to relieve menopausal symptoms, enhance fertility in women with progesterone deficiency or luteal phase defects, and aid the expulsion of the placenta after birth, reduce fibroids and normalise hormones following the use of oral contraceptives.
- Traditionally, it is described as a galactagogue (i.e. a medicine able to increase milk production in lactation) and is used in low doses for this indication.
- A mechanism of action has not been conclusively identified, but it appears to inhibit prolactin release by selective stimulation of pituitary dopamine D_2 receptors, increase progesterone levels and works via the opiate system.

PATIENTS' FAQs

What will this herb do for me?

Vitex is used to relieve common symptoms of PMS, such as irritability, mood swings, breast tenderness, headache and constipation. It is also used in combination with other herbal medicines to enhance fertility, relieve menopausal symptoms, regulate irregular menstruation, improve acne and promote milk production in new mothers.

When does it start to work?

Most trials show that treatment for at least three menstrual cycles may be required before symptom relief is experienced in PMS.

Are there any safety issues?

In cases of irregular menstruation, investigation for serious pathology should be undertaken before use of this herb.

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Chickweed

HISTORICAL NOTE Chickweed is one of the most common weeds worldwide. It has been used since ancient times to treat external inflammatory conditions and is also used as a tasty and nutritious vegetable, as well as poultry fodder to improve egg production.

COMMON NAME
Chickweed

OTHER NAMES
Mouse-ear, star chickweed, starweed, satinflower, starwort, stellaria, winterweed

BOTANICAL NAME/FAMILY
Stellaria media (family Caryophyllaceae)

PLANT PARTS USED
Aerial parts — leaves, stems and flowers

CHEMICAL COMPONENTS
Saponins, coumarins, flavonoids, carotenoids, carboxylic acids, as well as nitrate salts, vitamin C, calcium, iron, vitamins A and C and B-complex vitamins (Fisher & Painter 1996). Chromatography isolates include apigenin 6-C-beta-D-galactopyranosyl-8-C-alpha-L-arabinopyranoside, apigenin 6-C-alpha-L-arabinopyranosyl-8-C-beta-D-galactopyranoside, apigenin 6-C-beta-D-galactopyranosyl-8-C-beta-L-arabinopyranoside, apigenin 6-C-beta-D-glucopyranosyl-8-C-beta-D-galactopyranoside, and apigenin 6,8-di-C-alpha-L-arabinopyranoside (Dong et al 2007).

Chickweed essential oil has been found to contain several well-known contact allergens: borneol, menthol, linalool, 1,8-cineole, and other terpenes such as epoxy-dehydro-caryophyllene, monoterpene alcohol-ester and caryophyllene (Jovanović et al 2003).

MAIN ACTIONS
The pharmacological actions of chickweed have not been significantly investigated, so traditional use and an understanding of the actions of individual constituents is used.

Internal use — antitussive, expectorant and demulcent effects
Herbal saponins are well known to irritate mucous membranes and are successfully used as expectorants (e.g. senega). Herbs, such as chickweed, that

contain saponins are also suspected to have a degree of expectorant activity when used internally; however, this has not been investigated in controlled studies.

External use — soothing irritated skin and enhancing wound healing

Chickweed is traditionally thought to have soothing properties when applied to the skin in an appropriate vehicle, although controlled studies are not available to confirm these effects. The saponin content may account for the herb's ability to help reduce itchiness.

OTHER ACTIONS

An in vitro study identified that a chickweed decoction had activity against human hepatoma cell lines (Lin et al 2002). An ethanolic extract of chickweed has been found to strongly inhibit xanthine oxidase in vitro, suggesting that it may have a use against hyperuricaemia and gout (Pieroni et al 2002).

CLINICAL USE

Chickweed has not been significantly investigated under clinical trial conditions, so evidence is derived from traditional, in vitro and animal studies.

Urticaria, eczema, rashes, burns

Chickweed is most commonly used in external preparations for inflamed and itchy skin conditions such as urticaria, eczema, insect bites and stings, as well as minor wounds and cuts. Anecdotal evidence suggests that it may have some effects; however, controlled studies are not available to confirm effectiveness.

Bronchial phlegm and bronchitis

Taken orally, chickweed is often combined with other herbs for treating conditions characterised by fever and bronchial phlegm; however, controlled studies are not available to confirm effectiveness.

OTHER USES

Chickweed can be eaten raw in salads, served as cooked greens, juiced or infused as a tea. It has also been used as a mild laxative and diuretic substance.

DOSAGE RANGE

- Tincture (1:5): 2–10 mL three times daily.
- Infusion of dried herb: 1–5 g three times daily.
- Chickweed is commonly incorporated into a topical ointment or cream base for external use (1 part chickweed to 5 parts base) and applied as required.

TOXICITY

Allergic skin reactions can occur with topical use.

ADVERSE REACTIONS

There is insufficient reliable information available about the safety of chickweed when used internally or externally. Allergy to chickweed causing contact erythema multiforme has been reported (Jovanović et al 2003), and it is advised to apply a test patch to a small area before applying more widely.

SIGNIFICANT INTERACTIONS

Not known.

CONTRAINDICATIONS AND PRECAUTIONS

Allergic skin reactions can occur with topical use.

PREGNANCY USE

Likely to be safe when consumed in dietary amounts; however, safety is not known when used in larger quantities.

PRACTICE POINTS/PATIENT COUNSELLING

- Chickweed has been traditionally used as an ingredient in herbal creams and ointments to soothe inflamed, itchy skin and promote wound healing. Although controlled studies are unavailable, the pharmacological actions of several constituents within the herb suggest that it may be useful.
- Although it is likely to be safe, it is prudent to avoid using chickweed in pregnancy in amounts greater than those ingested when used as a food.

PATIENTS' FAQs

What will this herb do for me?

When chickweed is applied topically it may soothe inflamed and itchy skin. It is taken orally as a cough suppressant and expectorant.

How quickly will it work?

In practice, topical preparations are reported to produce symptom relief within 30 minutes; however, there are no controlled trials to confirm this.

Are there any safety issues?

Chickweed can be consumed as a food in salads, cooked as greens or prepared as a juice; however, the safety of larger intakes is unknown. Used as part of a herbal cream, it is likely to be safe, although it would be wise to do a test patch in a small area before applying to large areas. The safety of large doses in pregnancy is unknown.

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Chitosan

HISTORICAL NOTE With the exception of cellulose, chitin is the most abundant natural polysaccharide on Earth. It is produced by different crustaceans, molluscs, insects, algae, fungi and yeasts. Recently, the commercial value of chitin has increased because of the beneficial properties of its soluble derivatives, which are used in chemistry, biotechnology, agriculture, food processing, cosmetics, veterinary science, medicine, dentistry, environmental protection, and paper or textile production. The most useful chitin derivative is chitosan.

BACKGROUND AND RELEVANT PHARMACOKINETICS

Chitosan is a form of poorly soluble fibre, chemically derived from chitin, which is extracted from the exoskeletons of crustaceans or squid. It is a cationic polysaccharide and is in itself a major source of the nutritional supplement, glucosamine. Similar to other forms of fibre, such as oat bran, chitosan is thought to bind bile acids and dietary lipids. The solubility, biocompatibility and immunological activity and physicochemical properties of chitosan are altered by its molecular weight and degree of N-acetylation. The most biologically effective products contain a chitosan fraction with a low molecular weight, about 8 kD (Synowiecki & Al-Khateeb 2003).

The solubility of chitosan increases in the acidic environment of the stomach, but at a pH above 6.3 (e.g. in the intestines) the amino groups of chitosan and fatty acids, bile acids, cholesterol and lipids form a complex (Ylitalo et al 2002), and the resultant decreased availability of bile acids limits intestinal emulsification and the absorption of lipids, which are then excreted in the faeces.

CHEMICAL COMPONENTS

Chitosan is a cationic polysaccharide prepared by N-deacetylation of chitin.

DEFICIENCY SIGNS AND SYMPTOMS

Chitosan is not an essential nutrient, so deficiencies do not occur.

MAIN ACTIONS

Binds to fat

As it passes through the digestive tract, chitosan binds to ingested fat, bile acids, cholesterol and other lipids, preventing their absorption. The complexes that form between chitosan and various fats are then excreted in the faeces. A human study investigating whether the effect is clinically significant found that a dose of 4.5 g/d, taken in divided doses 30 min before meals, trapped only negligible amounts of fat as measured by fat excretion in stools (Gades & Stern 2003).

Antibacterial and antifungal activity

Animal studies have identified antibacterial activity against *Bifidobacterium* and *Lactobacillus*, which are part of the normal flora of the intestinal tract (Tanaka et al 1997). Clinical trials with a chitosan mouthwash and chewing gum have shown antibacterial activity against *Streptococcus mutans* (Sano et al 2003). Chitosan also inhibits the adhesion of *Candida albicans* to human buccal cells and has antifungal activity (Senel et al 2000).

OTHER ACTIONS

Chitosan can also absorb urea and ammonia and generally displays similar actions to other dietary fibres (Hendler & Rorvik 2001).

CLINICAL USE

The most biologically effective products contain a chitosan fraction having a low molecular weight. Unfortunately, not every clinical study indicates whether low-molecular-weight chitosan has been used. Therefore, aside from the usual variables, discrepant results may be due to differences in the type of chitosan used.

Weight loss

Chitosan is widely marketed as a weight loss aid, primarily due to its ability to bind to fats and reduce their absorption in the digestive tract.

A Cochrane systematic review published in 2005 analysed the results of 14 randomised studies involving 1131 subjects and concluded that use of chitosan resulted in a significantly greater weight loss, decrease in total cholesterol and decrease in systolic and diastolic blood pressure than placebo (Ni et al 2005). The studies had a minimum duration of 4 weeks and were conducted with overweight or obese subjects. With regard to the frequency of adverse events or faecal fat excretion, no clear differences were observed between the placebo and chitosan groups. Although encouraging, the authors noted that the quality of the studies was suboptimal and overall results were variable. A look at the studies of highest quality suggests that the effects are minimal. The mean trial duration was 8.3 weeks (range 4–24 weeks) and eight of the 14 studies combined the use of chitosan or placebo with a low-calorie or weight-reducing diet. Interpretation of the data is not straightforward because the dose of chitosan used in studies varied considerably, from 0.24 g/day to 15 g/day (mean 3.7 g/day) and six of the studies used treatment preparations that contained other active ingredients in addition to chitosan. Additionally, the review excluded some potentially important trials because they did not meet criteria for inclusion (e.g. subjects were not enrolled for being overweight but selected for other reasons).

In 2008, an updated Cochrane systematic review was published which evaluated 15 clinical studies (n = 1219) (Jull et al 2008). Analyses indicated that

chitosan preparations result in a significantly greater weight loss (weighted mean difference −1.7 kg; $P < 0.00001$), decrease in total cholesterol (−0.2 mmol/L; $P < 0.00001$), and a decrease in systolic and diastolic blood pressure compared with placebo. Chitosan treatment was well tolerated, as there were no clear differences between intervention and control groups in terms of frequency of adverse events or in faecal fat excretion. Whilst these results are encouraging, reviewers once again reported that the quality of many studies was suboptimal and analysis of only high quality trials yielded less convincing evidence.

Previously, a 1998 meta-analysis identified five studies evaluating the effectiveness of chitosan for the treatment of obesity (Ernst & Pittler 1998). All studies included were conducted in Italy and published in a single Italian journal over a 2-year period. They concluded that the mean difference in terms of weight reduction between chitosan and placebo was approximately 3.3 kg. It is worth noting that these five studies consistently demonstrated the greatest effects in the 2005 Cochrane systematic review discussed above, were all of short duration, and four of them also included other agents in the chitosan preparations.

A later systematic review conducted by Ernst and Pittler, which included five additional studies, concluded that when these new results were combined with the previous five from the 1998 meta-analysis, the evidence becomes less compelling and raised doubts about the effectiveness of chitosan in weight loss (Pittler & Ernst 2004).

Clearly, further well-reported research is required, using longer time frames and clearly stating the composition of the chitosan preparations.

Hyperlipidaemia

The ability of chitosan to form complexes with various fats, including cholesterol, provides a theoretical basis for its use in hyperlipidaemia. Dietary chitosan has been tested and found to be effective in reducing serum cholesterol levels and atherosclerosis in normal and diabetic mice, and, therefore, has been investigated in the treatment of hypercholesterolaemia in humans (Muzzarelli 1999).

A 2002 review states that in humans, dietary chitosan reduces serum total cholesterol levels by 5.8–42.6% and LDL levels by 15.1–35.1% (Ylitalo et al 2002). Based on these figures, the effects of chitosan range from mild to moderate and appear to be inconsistent for total cholesterol. More specifically, lowering of LDL cholesterol is more consistent, whereas little effect is seen on plasma triglyceride concentration, according to several different experimental and human studies involving obese or diabetic subjects or people with mild to moderate hypercholesterolaemia (Bokura & Kobayashi 2003, Tai et al 2000, Wuolijoki et al 1999, Yihua & Binglin 1997).

Reduction in LDL cholesterol was evident after 4 weeks' treatment with a microcrystalline chitosan (1.2 g twice daily) according to one double-blind study (Wuolijoki et al 1999) and after 8 weeks' treatment using a low dose of 1.2 g/day of chitosan in another double-blind study (Bokura & Kobayashi 2003). However, not all studies have produced positive results. One double-blind study found no effect with 1.5 g chitosan tablets taken three times daily (Zahorska-Markiewicz et al 2002). More recently, no significant effect on total cholesterol, LDL cholesterol or triglycerides was seen in a randomised placebo controlled study, which tested chitosan capsules (1 g twice daily) (Guha et al 2005). The group receiving chitosan did report a significant reduction in mean body weight (3.14% versus 1.29% of body weight, $P < 0.05$) and a significant rise in HDL cholesterol value (3.8% versus 1.07%, $P = 0.02$).

The electrically neutral nature of triglycerides may mean that chitosan is unable to form complexes with it, and, therefore, is unable to influence its absorption.

In contrast, a more recent 2008 study found no significant effects on total cholesterol levels or LDL cholesterol concentration for chitosan after 8 weeks of treatment (Tapola et al 2008). The randomised study involved 65 men and women and compared the effect of two different doses of chitosan to placebo on serum fat-soluble vitamin concentrations, cholesterol concentrations, and other safety parameters (Tapola et al 2008). The doses of chitosan tested were 0, 4.5 or 6.75 g/d and the placebo consisted of 6.75 g/d glucomannan. In addition, no treatment induced a change in levels of serum vitamins (vitamin A, vitamin E, 25-hydroxyvitamin D), carotenes (alpha- and beta-carotene).

Dental plaque prevention

Considering that chitosan has antibacterial activity against *Streptococcus mutans* and antifungal action against *Candida albicans*, it has been added to mouthwashes and gels for dental use. One randomised, crossover clinical trial involving 24 volunteers found that rinsing with a mouthwash containing 0.5% chitosan for 14 days was significantly more effective in reducing plaque formation than placebo (Sano et al 2003). Several clinical studies have investigated the effect of chitosan-containing chewing gum. One clinical study reported that chewing the gum significantly decreased oral bacterial counts and significantly increased salivary secretion (Hayashi et al 2007a). Another confirmed antibacterial activity for the gum, especially reducing total streptococci, mutans streptococci in saliva (Hayashi et al 2007b). Hayashi et al suggested that chewing chitosan-containing gum could be an effective method for controlling the number of cariogenic bacteria in situations where it is difficult for a person to brush their teeth. The gum used in the study was xylitol-based and supplemented with chitosan so it dissolved in saliva at a rate of about 2% (w/v).

Periodontal disease

Chitosan was tested as both a carrier in gel form for the antibiotic metronidazole and as an active agent in the treatment of chronic periodontitis (CP) (Akncbay et al 2007). The chitosan gel (1% w/w) incorporated with or without 15% metronidazole was prepared and applied adjunctive to

scaling and root planing (SRP) and compared to SRP alone (control group-C), in CP patients. All groups experienced significant improvements for clinical parameters between baseline and week 24 ($P < 0.05$). Chitosan was found to be effective in itself as well as in combination with metronidazole in CP treatment due to its antimicrobial properties.

Kidney failure

One open study of 80 patients with renal failure, undergoing haemodialysis, found that 1350 mg of chitosan taken three times daily effectively reduced total serum cholesterol levels (from 10.14 ± 4.40 mmol/L to 5.82 ± 2.19 mmol/L) and increased serum haemoglobin levels (from 58.2 ± 12.1 g/L to 68 ± 9.0 g/L) (Jing et al 1997). After 4 weeks, significant reductions in serum urea and creatinine levels were observed. After 12 weeks, patients reported subjective improvements, such as feeling physically stronger, increased appetite and improved sleep, which were also significantly greater than the placebo group. Importantly, during the treatment period, no clinically problematic symptoms were observed.

Wound healing — topical use

Chitosan is applied to burns and wound dressings in the form of films, bandages, cotton-like materials and non-woven napkins. These dressings have good hydroscopicity, show high bacteriostatic effect and are completely biodegradable in the human body. Another significant advantage is that repeated dressings are usually not needed (Synowiecki & Al-Khateeb 2003). Topical application of chitosan enhances wound healing and has been used to promote donor-site tissue regeneration in plastic surgery. Its use is supported by findings that indicate chitosan accelerates the reformation of connective tissue (Ueno et al 2001).

OTHER USES

Drug delivery systems

Chitosan is considered a good carrier for the controlled release of drugs over an extended period of time (Synowiecki & Al-Khateeb 2003). Additionally, it has been shown to excel in transcellular transport.

Chitosan is also used as a component of different cosmetics, toothpaste, hand and body creams and hair-care products (Synowiecki & Al-Khateeb 2003).

DOSAGE RANGE

- The standard dose of chitosan is 3–6 g/day, taken with food.

According to clinical studies

- Weight loss: 3.0–4.5 g taken daily in divided doses, 30 minutes before meals.
- Hyperlipidaemia: 1.2–4.5 g/day in divided doses.
- Dental plaque prevention: rinse daily with mouthwash containing 0.5%.
  - Periodontal disease: chitosan gel (1% w/w) applied as an adjunct to scaling and root planing.
- Renal failure: 1.35 g taken three times daily.

Clinical note — Periodontal disease

Periodontal disease is a collective term used to describe several pathological conditions characterised by degeneration and inflammation of gums, periodontal ligaments, alveolar bone and dental cementum. It is a localised inflammatory response caused by bacterial infection of a periodontal pocket associated with subgingival plaque. Periodontal disease has been considered as a possible risk factor for other systemic diseases such as cardiovascular diseases and preterm, low-birth-weight infants. Increasingly, chitosan is being used as a polymeric matrix in the form of film enriched with taurine (antioxidant agent). Taurine enhances the wound healing ability of chitosan and is considered beneficial in tissue repair in destructive diseases like periodontitis (Jain et al 2008).

ADVERSE REACTIONS

A systematic review of 14 randomised studies found that the most common side effects reported were constipation, nausea, bloating, indigestion and abdominal pain (Ni et al 2005). Increased water consumption may reduce some of these side effects.

Overall, chitosan is considered very safe and well tolerated according to safety studies in experimental models (Kim et al 2001).

SIGNIFICANT INTERACTIONS

Fat-soluble nutrients

Considering chitosan binds to dietary fats and reduces their absorption, chitosan can also affect the absorption of fat-soluble vitamins. However, the effect may be dose dependent as one study using a dose of 2 g/day found no changes to the levels of vitamins A, D, E and beta-carotene after 4 weeks' use (Pittler et al 1999). A more recent study confirmed that there were no significant effects on serum vitamins (vitamin A, vitamin E, 25-hydroxyvitamin D) and carotenes (alpha- and beta-carotene) with oral chitosan after 8 weeks even at a dose of 6.75 g daily (Tapola et al 2008).

Lipophilic drugs

Considering chitosan binds to dietary fats and reduces their absorption, chitosan can also affect the absorption of lipophilic drugs. Separate doses by at least 2 hours.

Vitamin C

According to a preliminary study in rats, taking vitamin C together with chitosan might provide additional benefit in lowering cholesterol.

CONTRAINDICATIONS AND PRECAUTIONS

Chitosan is contraindicated in people with allergies to shellfish.

PREGNANCY USE

Pregnant women should avoid chitosan as it may reduce absorption of essential dietary nutrients.

PRACTICE POINTS/PATIENT COUNSELLING

- Chitosan is a form of poorly soluble fibre, chemically derived from chitin, which is extracted from the exoskeletons of crustaceans or squid. The most biologically active forms have a low molecular weight.
- It forms insoluble complexes with dietary fats, fatty acids, bile acids, cholesterol and other lipids in the digestive tract and has antibacterial and antifungal activity that is useful in dental hygiene.
- Chitosan is a popular weight loss supplement. Clinical studies have produced mixed results; however, best effects occur when chitosan is used over several months and combined with dietary and lifestyle modifications.
- Overall, evidence generally supports its use in hyperlipidaemia, as it reduces serum levels of total cholesterol and LDL levels, but it has little effect on triglyceride levels.
- Chitosan is contraindicated in people with allergies to shellfish and should be recommended together with a multivitamin supplement with long-term use.

PATIENTS' FAQs

What will this supplement do for me?

Taken orally, chitosan may aid in weight loss when combined with dietary and lifestyle modifications and may reduce cholesterol levels.

When will it start to work?

Effects in weight loss require at least 8 weeks' continual use before effects are seen, according to research, whereas cholesterol lowering requires 4–8 weeks.

Are there any safety issues?

Chitosan is contraindicated in people with allergies to shellfish.

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Chondroitin

OTHER NAMES

Chondroitin sulfate, chondroitin sulfuric acid, chondroitin 4-sulfate, chondroitin 4- and 6-sulfate

BACKGROUND AND RELEVANT PHARMACOKINETICS

Chondroitin sulfate is an amino sugar polymer, made up of glucuronic acid and galactosamine that is in the class of large polymers known as glucosaminoglycans or mucopolysaccharides. These compounds act as the flexible connecting matrix between the protein filaments in cartilage and connective tissue (Liesegang 1990). It has been found that serum levels of chondroitin sulfate are increased in patients with both rheumatoid arthritis and osteoarthritis and this may provide the basis for systemic detection of osteoarthritis (Pothacharoen et al 2006).

Chondroitin sulphate molecules represent a heterogeneous population the structure of which varies with source, manufacturing processes, presence

of contaminants, and other factors and, thus, there are a range of structures with differing potential for therapeutic impacts on a range of pathologies (Lauder 2009). There are also differences in the absorption and bioavailability of chondroitin formulations due to differences in molecular mass, charge density, and cluster of disulfated disaccharides of the parental molecules (Volpi 2003). This has led to a call for reference standards having high specificity, purity and well-known physicochemical properties useful for accurate and reproducible quantitative analyses (Volpi 2007).

Chondroitin is generally manufactured from natural sources, such as shark and bovine (usually tracheal) cartilage and may have a molecular weight that varies from 10 to 50 kD, depending on the product's source or preparation (Ross 2000). Low-molecular-weight chondroitin appears to be absorbed orally in both animals and humans (Adebowale et al 2002, Du et al 2004) and displays accumulation after multiple dosing (Adebowale et al 2002). Chondroitin is concentrated in the intestine, liver, kidneys, synovial fluid and cartilage (Conte et al 1995) and the elimination half-life is about 5–6 hours, with 40–50% being excreted in the urine (Conte et al 1991, Ronca & Conte 1993). Oral chondroitin is absorbed as several metabolites, and as the active moiety has not yet been identified it is difficult to establish bioequivalence between different products (Volpi 2003).

CHEMICAL COMPONENTS

Chondroitin sulfate is a linear polymer of two alternating sugars, alpha-D-N-acetylgalactosamine and beta-D-glucuronic acid, with the sulfate moiety being a covalent part of the molecule and not a counter ion as is the case with glucosamine sulfate (Ross 2000).

FOOD SOURCES

Chondroitin is naturally present in the gristle in meat. As a supplement it is generally produced from natural sources, such as shark or bovine (usually tracheal) cartilage or can be manufactured in the laboratory using various methods. The purity and content of products have been questioned in the USA, where it is regarded as a nutritional supplement and its quality is unregulated (Consumer-lab 2009).

MAIN ACTIONS

Chondroprotective effect

Chondroitin appears to protect cartilage by providing it with the raw material required for repair, as well as inhibiting the enzymes in synovial fluid, such as elastase and hyaluronidase, that damage joint cartilage. It improves chondrocyte nutrition by increasing hyaluronic acid production in articular cells (Raoudi et al 2005) and, hence, the fluid content of the extracellular matrix (Sasada et al 2005), which not only acts as a shock absorber but also brings nutrients into the cartilage (Krane & Goldring 1990). In vitro studies have shown that low dose combinations of glucosamine hydrochloride and chondroitin sulfate stimulate collagen and non-collagenous protein synthesis by ligament cells, tenocytes and chondrocytes (Lippiello 2007). An overall chondroprotective effect of chondroitin has also been demonstrated in different animal models. In a rabbit model oral or intramuscular chondroitin sulfate was shown to protect articular cartilage from experimental chymopapain injury (Uebelhart et al 1998a) and inhibit the destruction of the cartilage extracellular matrix (Sumino et al 2005). In a dog model, chondroitin sulfate was seen to stimulate articular cartilage and decrease or delay the alterations of degenerative joint disease (Melo et al 2008). In other animal models, co-administration with glucosamine was shown to prevent both biochemical and histological alterations and provide pain reduction (Silva et al 2009).

It has been suggested that at least some of the chondroprotective action of chondroitin sulfate is due to the provision of a source of additional inorganic sulfur which is essential for glycosaminoglycan (GAG) synthesis as well as being a structural component of glutathione and other key enzymes, coenzymes and metabolites that play fundamental roles in cellular homeostasis and control of inflammation (Nimni et al 2006). This is supported by the finding that chondroprotective action of chondroitin is potentiated by high sulfur mineral water (Caraglia et al 2005).

Anti-inflammatory

Chondroitin exerts an anti-inflammatory action with an inhibitory effect over complement (Pipitone 1991). In an in vitro study of bovine cartilage, chondroitin alone, and in combination with glucosamine, was found to regulate gene expression and synthesis of NO and PGE_2, suggesting a basis for its anti-inflammatory properties (Chan et al 2005). Chondroitin sulfate has been found to increase the levels of antioxidant enzymes and reduce inflammation and cirrhosis of liver tissue in an ovariectomised rat model, suggesting that it enhances antioxidant activity (Ha 2004). It has been suggested that chondroitin's multiple anti-inflammatory effects in chondrocytes and synoviocytes are primarily due to a common mechanism, through the inhibition of NF-ϰB nuclear translocation (Iovu et al 2008).

Viscoelastic agent

Chondroitin sulfate is a viscoelastic agent and together with similar substances such as sodium hyaluronate and hydroxypropyl methylcellulose, is used in ophthalmic surgery to protect and lubricate cells and tissues (Larson et al 1989, Liesegang 1990).

OTHER ACTIONS

There are suggestions from laboratory studies and uncontrolled human trials that chondroitin may have potential antiatherogenic properties (Morrison 1969, 1971, Morrison & Enrick 1973).

A review of the potential therapeutic applications of chondroitin sulfate/dermatan sulfate suggest that chondroitin sulfate may have potential applications in parasitic and viral infections, regenerative medicine and development of antitumour therapies (Yamada & Sugahara 2008).

CLINICAL USE

Osteoarthritis (OA): symptom control and retarding disease progression

There are now a number of reviews and meta-analyses of clinical data (Bruyere & Reginster 2007, Monfort et al 2008, Uebelhart 2008, Vangsness et al 2009), including a critical appraisal of five separate meta-analyses (Monfort et al 2008), which suggest that oral chondroitin sulfate is a valuable and safe symptomatic treatment for OA disease. Chondroitin sulfate appears to produce a slow but gradual reduction of the clinical symptoms of OA. Multiple human clinical trials lasting from a few weeks to 3 years have shown that chondroitin sulfate can significantly alleviate symptoms of pain and improve function in patients with OA of the knee, finger and hip (Bourgeois et al 1998, Bucsi & Poor 1998, Fioravanti et al 1991, Lazebnik & Drozdov 2005, Mazieres et al 2001, Morreale et al 1996, Oliviero et al 1991, Rovetta 1991, Uebelhart 2008) and that these effects last months after the cessation of treatment (Mazieres et al 2005), as well as being evident with intermittent treatment (Uebelhart et al 2004).

There is also evidence from double-blind clinical trials that chondroitin can reverse, retard or stabilise the pathology of OA (Volpi 2005), as evidenced by stabilisation of the joint space (Uebelhart et al 1998b), less progression of erosions (Rovetta et al 2002, Verbruggen et al 1998) and improved articular cartilage thickness (Pipitone et al 1992) and interarticular space, as observed by X-rays (Conrozier 1998, Michel et al 2005, Uebelhart et al 2004). A subanalysis of patients involved in the Glucosamine/Chondroitin Arthritis Intervention Trial (GAIT) study (see below and Glucosamine monograph) further suggests that chondroitin sulfate may have differential effects on OA symptoms depending on the degree of radiographic involvement, and that chondroitin may provide improvements in knee pain in patients with relatively early radiographic disease (Clegg et al 2005). In contrast to the above findings, a 24-month, double-blind, placebo-controlled study of 572 patients conducted as part of the GAIT study did not demonstrate reductions in joint space narrowing although there was a trend for improvement in knees with K/L grade 2 radiographic OA. The authors state, however, that power of this study was diminished by the limited sample size, variance of joint space width (JSW) measurement, and a smaller than expected loss in JS (Sawitzke et al 2008).

Comparisons with NSAIDs

Although chondroitin appears to be at least as effective as non-steroidal anti-inflammatory drugs (NSAIDs) in treating the symptoms of OA (Fioravanti et al 1991, Morreale et al 1996), it has a slower onset of action, taking 2–4 months to establish an effect (Leeb et al 2000, Morreale et al 1996). Chondroitin may, however, provide benefits that persist after treatment is stopped (Mazieres et al 2001, Morreale et al 1996).

Combined use of chondroitin sulfate and glucosamine sulfate

Chondroitin and glucosamine are frequently marketed together in combination products and some studies suggest that this combination is effective in treating symptoms (Das & Hammad 2000, Leffler et al 1999, McAlindon et al 2000, Nguyen et al 2001) and reducing joint space narrowing (Rai et al 2004). These findings are supported by an in vitro study on horse cartilage that found that a combination of glucosamine and chondroitin was more effective than either product alone in preventing articular cartilage glycosaminoglycan degradation (Dechant et al 2005), as well as an in vivo study on rats that found that the combined treatment prevented the development of cartilage damage and was associated with a reduction in IL-1-beta and matrix metalloprotease-9 synthesis (Chou et al 2005). The recent GAIT trial (see Glucosamine monograph) provides further evidence that glucosamine and chondroitin are more effective when given in combination than when either substance is given alone, with the combined treatment being more effective than the cyclooxygenase-2 (COX-2) inhibitor, celecoxib, for treating moderate to severe arthritis compared with chondroitin alone (Clegg et al 2006).

A small, randomised controlled trial (RCT) has suggested that the addition of high-molecular-weight hyaluronate to glucosamine and chondroitin may provide additional benefits to the use of glucosamine and chondroitin alone (Bucci et al 2005).

Topical preparations

A topical preparation containing chondroitin with glucosamine and camphor has been shown to reduce pain from osteoarthritis of the knee in one RCT (Cohen et al 2003).

OTHER USES

Heart disease

There are suggestions that chondroitin in doses of up to 10 g/d may have antiatherogenic actions, beneficial effects on serum lipid levels and may be useful for reducing the risk of myocardial infarction (Morrison 1969, 1971, Morrison & Enrick 1973, Morrison et al 1969).

Snoring

The results of a pilot crossover study of seven subjects suggest that chondroitin sulfate instilled into the nostril at bedtime may reduce snoring (Lenclud et al 1998).

Ophthalmic surgery and dry eyes

Chondroitin sulfate is used as a viscoelastic substance to protect and lubricate cells and tissues during ophthalmic surgery, as well as to preserve corneas before transplantation (Larson et al 1989, Liesegang 1990). In a double-blind, crossover study of 20 subjects, 1% chondroitin sulfate was found to be as effective as polyvinyl alcohol artificial tear formulation and 0.1% hyaluronic acid in reducing itching, burning and foreign body sensation

in people with keratoconjunctivitis sicca (Limberg et al 1987).

Psoriasis

It has been found that some patients with psoriasis experience a significant clinical and histological improvement in their psoriatic lesions after taking chondroitin to treat their OA (Verges et al 2004, 2005).

Interstitial cystitis

A multicentre, community-based clinical practice study suggests that intravesical chondroitin sulphate may have an important role in the treatment of interstitial cystitis (Nickel et al 2009).

DOSAGE RANGE

- Oral doses of chondroitin range from 800–1200 mg/day in either single or divided doses. Intramuscular, intravenous and topical forms are also available.
- A 4–5-month trial is generally used in order to determine whether it is effective for an individual patient.
- A dose-finding study in patients with knee osteoarthritis suggests that administration of 800 mg of chondroitin sulfate orally had nearly the same effects as 1200 mg/day, while the use of a sequential 3 months administration mode, twice a year was also shown to provide the same results as a continuous treatment (Uebelhart 2008).

ADVERSE REACTIONS

Chondroitin is generally deemed to be extremely safe, with the incidence of adverse reactions being comparable to placebo in studies lasting from 2 months to 6 years (Bourgeois et al 1998, Bucsi & Poor 1998, Hathcock & Shao 2007, Leeb et al 2000, McAlindon et al 2000, Uebelhart et al 1998b, Vangsness et al 2009).

Oral chondroitin may cause mild gastrointestinal disturbance. While there is a theoretical risk of anticoagulant activity, this has not been demonstrated in clinical trials (Chavez 1997) and chondroitin has been assessed as having a complete absence of adverse effects and an observed safe level (OSL) at doses of up to 1200 mg/day (Hathcock & Shao 2007).

SIGNIFICANT INTERACTIONS

Controlled studies are not available; therefore, interactions are based on evidence of activity and are largely theoretical and speculative.

Anticoagulants

Additive effect theoretically possible — observe patient.

Non-steroidal anti-inflammatory drugs

Chondroitin may enhance drug effectiveness, suggesting a beneficial interaction is possible — drug dosage may require modification.

CONTRAINDICATIONS AND PRECAUTIONS

Due to theoretical anticoagulant activity, chondroitin should be used in caution in people with clotting disorders.

Some forms of chondroitin are produced from bovine (usually tracheal) cartilage, so it is theoretically possible that it may be a source of transmission of bovine spongiform encephalopathy (mad cow disease) and other diseases. This transmission has not been demonstrated and is deemed unlikely.

PREGNANCY USE

Insufficient reliable information available to advise on safety in pregnancy.

PRACTICE POINTS/PATIENT COUNSELLING

- Chondroitin is a naturally occurring building block of joint tissue and cartilage. Supplements are made from shark cartilage or bovine tracheal cartilage.
- Chondroitin is generally considered effective in treating the pain and disability of osteoarthritis and may act to slow disease progression, although it may take some weeks before a clinical effect is evident.
- It is considered extremely safe and may reduce the need for NSAIDs, which can have serious side effects.
- There may be benefits in taking chondroitin in conjunction with glucosamine for treating arthritis.
- Patients undergoing anticoagulant therapy or with clotting disorders should have their blood clotting monitored while taking chondroitin.

PATIENTS' FAQs

What will this supplement do for me?

Multiple scientific studies have shown that chondroitin sulfate reduces symptoms of OA and may also reduce further progression of the condition. Some people find that they do not require NSAIDs as often when taking it.

When will it start to work?

Symptom relief takes 2–4 months to reach maximal effect, but protection effects on the joints occur only with long-term use of several years.

Are there any safety issues?

Generally considered a very safe treatment and far safer than pharmaceutical anti-inflammatory drugs; however, it should be used with caution by people with clotting disorders or taking anticoagulants.

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Chromium

HISTORICAL NOTE In the 1950s, researchers identified the role of chromium in insulin and glucose control (Shwarz & Mertz 1959). The importance of chromium was validated in 1977 when a woman on long-term TPN, without chromium, developed symptoms of diabetes that could not be controlled by insulin. After further investigation it was noted that she was deficient in chromium and when < 50 μg was added to her TPN solution, symptoms resolved. This led to the US FDA listing chromium as an essential trace nutrient (Edmonson 2002). However, problems in elucidating the effects of chromium supplementation persist, due to a lack of practical methods for diagnosing deficiency (Mertz 1998). In recent years researchers have focused on investigating the effects of chromium supplementation on insulin sensitivity and the management and prevention of type 2 diabetes and cardiovascular disease (Hummel et al 2007).

BACKGROUND AND RELEVANT PHARMACOKINETICS

Absorption of chromium occurs by passive diffusion and is inversely related to dietary intake (e.g. from a dose of 10 μg, 2% is absorbed; from a dose of 40 μg, 0.5% is absorbed) (Anderson & Kozlovsky 1985). Absorption may be inhibited by zinc (Hahn & Evans 1975) and phytates, and enhanced by oxalate (Bryson & Goodall 1983) and ascorbic acid (Offenbacher 1994). Unfortunately much of the current information is based on chromium chloride supplements so effects may vary for different forms (Arthur 2008). For instance the complexation of picolinic acid with chromium increases its bioavailability (Edmonson 2002, Press et al 1990). Nicotinic acid is also a metabolite of tryptophan improving the absorption of chromium; however, the picolinate form is the one surrounded by the most controversy.

Chromium is transported around the systemic circulation primarily by transferrin (Campbell et al 1997) potentially competing with iron, and accumulates in kidney, muscle and liver (Hepburn & Vincent 2003). It is excreted primarily in urine, but small amounts are lost in hair, perspiration and faeces.

CHEMICAL COMPONENTS

Chromium exists mostly in two valence states in nature: hexavalent chromium (chromium (VI)) and trivalent chromium (chromium (III)). The hexavalent form is used in industry and is associated with toxicity. Trivalent chromium is an essential trace element in the human body and approved as a supplement.

Supplemental forms used in trials include organic chromium complexes such as chromium picolinate and chromium nicotinate/polynicotinate (niacin-bound chromium NBC) and inorganic salts such as chromium chloride. While a number of different commercial trivalent chromium supplements exist the best evidence is

for the picolinate and polynicotinate forms (Preuss et al 2008).

FOOD SOURCES

Brewer's yeast, wholegrain breads and cereals, cheese, eggs, bananas, spinach, mushrooms, broccoli, organ meats and processed meat products.

DEFICIENCY SIGNS AND SYMPTOMS

Primary deficiency

Symptoms of weight loss, glucose intolerance and neuropathy have been noted in patients on TPN deficient in chromium (Verhage et al 1996). Deficiency may also be a precursor to the development of insulin resistance, and thus associated with hyperglycaemia, hypoglycaemia and obesity. Up to 90% of USA diets have been found to be below the minimum suggested safe and adequate daily intake for chromium of 50 μg/day (Anderson & Kozlovsky 1985).

Secondary deficiency

Factors that may exacerbate deficiency, generally by increasing requirements for or urinary excretion of chromium, include pregnancy, excessive exercise, infection, physical trauma and stress (Anderson 1986). Diets high in simple sugars have been found to increase urinary chromium excretion up to 30-fold, thereby increasing the risk of deficiency (Kozlovsky et al 1986). Corticosteroids also increase urinary losses of chromium (Kim et al 2002).

MAIN ACTIONS

Important cofactor

Chromium is an essential trace mineral required for carbohydrate, lipid, protein and corticosteroid metabolism (Kim et al 2002). It is a key constituent of glucose tolerance factor, together with nicotinic acid and the amino acids cysteine, glycine and glutamic acid.

Clinical note — Problems testing for chromium deficiency

Currently, testing for chromium deficiency involves serum testing. This is problematic as it is still uncertain whether serum levels correlate with tissue levels and, therefore, are truly representative of nutritional status. Studies have shown that subjects with widely varying plasma chromium levels respond favourably to chromium supplementation, suggesting that this marker is misleading (Bahijri 2000). As a consequence, serum tests should not be solely relied upon, leaving the diagnosis of marginal deficiency up to a practitioner's clinical suspicion. Other tests have been proposed such as toenail chromium concentration (Guallar et al 2005) and urinary chromium response to glucose load (Bahijri & Mufti 2002), as conditions that increase circulating glucose and insulin concentrations increase urinary chromium output (Vincent 2004); however, further research is required to confirm the validity of these tests.

Improves blood sugar control

Trivalent chromium is an essential trace element for normal carbohydrate metabolism and insulin sensitivity (Wilson & Gondy 1995), aiding the transport of glucose into cells. Rather than increasing insulin secretion, chromium appears to improve glycaemic control by enhancing the action of insulin; improving the ability of insulin to bind to cells; enhancing beta-cell sensitivity; increasing the number of insulin receptors; and activating insulin receptor kinase, thus increasing insulin sensitivity (Anderson 1997, Edmonson 2002). Additionally, in vitro studies have shown that chromium inhibits the secretion of TNF-alpha, a cytokine known to reduce the sensitivity and action of insulin, and that this appears to be mediated by its antioxidant effects (Jain & Kannan 2001). In vitro studies also show that chromium chloride prevents the increase in protein glycosylation and oxidative stress caused by high levels of glucose in erythrocytes (Jain et al 2006).

Lipid-lowering activity

Although the mechanism of action is yet to be fully explained, studies show that chromium supplementation may decrease triglyceride levels, total and LDL-cholesterol and modestly increase HDL-cholesterol (Bahijri 2000, Lee & Reasner 1994, Press et al 1990, Preuss et al 2000).

Antihypertensive

In rats with sugar-induced blood pressure elevation, niacin-bound chromium lowers systolic blood pressure, at least in part due to its effects on the renin-angiotensin system (Perricone et al 2008).

Antidepressant/neurotransmitter effects

Depression is often associated with insulin resistance, owing to cortisol overproduction (McCarty 1994). The reputed antidepressant effects of chromium may be explained by improvements in insulin sensitivity (Davidson et al 2003) and related increases in tryptophan availability and/or noradrenaline release (McLeod & Golden 2000). Chromium has also been shown to lower the cortisol response to challenge with 5-hydroxy-L-tryptophan (5-HTP) and decrease the sensitivity of 5-HT_{2A} receptors (Attenburrow et al 2002). Influences on serotonergic pathways have also been reported in animal studies using chromium picolinate (Khanam & Pillai 2006) and potassium channels are thought to be involved.

OTHER ACTIONS

Immunomodulation

A review detailing the effects of chromium on the immune system found that chromium has both immunostimulatory and immunosuppressive effects, as shown by its effects on T and B lymphocytes, macrophages and cytokine production (Shrivastava et al 2002).

Bone density protection

It has been suggested that modulation of insulin by chromium may have positive effects on bone density, reducing bone resorption and promoting collagen production by osteoblasts (McCarty

1995). One placebo-controlled study using chromium picolinate (equivalent to 200 μg chromium/day for 60 days) has shown a 47% reduction in the urinary hydroxyproline:creatinine ratio, indicating a decrease in calcium excretion and a potential role in the prevention of osteoporosis (Evans et al 1995).

Antioxidant

A placebo-controlled trial using 1000 μg/day of chromium (as chromium yeast) for 6 months found chromium supplementation to be an effective treatment in reducing oxidative stress in type 2 diabetes patients with severe hyperglycaemia (HbA_{1c} > 8.5%); however, it may act as a pro-oxidant in euglycaemic people (Cheng et al 2004).

Anti-inflammatory

In diabetic rats, chromium supplementation can lower the risk of vascular inflammation. Chromium niacinate appears to be more effective than the picolinate form in lowering blood levels of pro-inflammatory cytokines (TNF-alpha, IL-6) and C-reactive protein, and in reducing oxidative stress and lipid levels (Jain et al 2007).

Increases dehydroepiandrosterone

In a placebo-controlled trial, chromium picolinate (equivalent to 200 μg chromium/day for 60 days) increased dehydroepiandrosterone by 24% in postmenopausal women (Evans et al 1995).

CLINICAL USE

Supplemental forms used in trials include organic chromium complexes, such as chromium picolinate and chromium nicotinate, and inorganic salts such as chromium chloride. Considering chromium is known to improve insulin sensitivity, a theoretical basis exists for its use in conditions associated with insulin resistance such as type 2 diabetes mellitus, gestational diabetes, hypoglycaemia, polycystic ovarian syndrome, obesity and syndrome X. For many of these indications, controlled studies are not yet available. However, there has been investigation into its use in diabetes, hypoglycaemia, hyperlipidaemia and obesity.

Deficiency states: prevention and treatment

Although chromium deficiency is uncommon (Vincent 2004) and mostly described in relation to the use of TPN without chromium, subclinical deficiency states also exist and should respond to supplementation (Verhage et al 1996). Chromium supplementation is also used in cases at risk of deficiency, such as long-term corticosteroid use (Kim et al 2002) or people with a high sugar intake (Kozlovsky et al 1986).

Diabetes

Subjects with diabetes appear to have lower tissue levels of chromium and a correlation exists between low circulating levels of chromium and the incidence of type 2 diabetes (Hummel et al 2007). While still controversial, a number of studies and reviews suggest that chromium supplementation may facilitate insulin signalling and therefore improve systemic insulin sensitivity. A review of 15 clinical studies involving a total of 1690 subjects (1505 of which received chromium picolinate) reported significant improvement in at least one outcome of glycaemic control. The pooled data showed substantial reductions in both hyperglycaemia and hyperinsulinaemia (Broadhurst & Domenico 2006).

A systematic review (Balk et al 2007) identified 41 trials meeting its inclusion criteria (English language; RCT; ≥ 3 weeks duration, ≥ 10 participants). The evidence was limited by 'poor study quality, heterogeneity in methodology and results, and a lack of consensus on assessment of chromium status'; and larger effects were generally reported in the poorer-quality studies. Differences in chromium formulations and dose may have in part accounted for the heterogeneous results. While studies using brewer's yeast demonstrated some increase in net effect, trials directly comparing formulations have not established a difference between the forms. A dose–effect response has also been reported with effects seen at doses of at least 200 μg chromium picolinate/day. Comparisons of 200 μg versus 1000 μg have shown greater effect at the highest dose but this is largely driven by the Anderson (1997) study results, see below. The review authors concluded that positive results with chromium supplementation are more likely in persons with known glycaemic aberrations rather than in healthy subjects (Balk et al 2007). Although it is uncertain why this is the case, the varying responses of glucose and lipid regulation may be partly explained by variations in pretreatment chromium and iron status, and phenotypic characteristics of the studied individuals. Furthermore, baseline insulin sensitivity may be particularly important in predicting a clinical response to chromium (Wang et al 2007).

Type 2 diabetes mellitus (non-insulin-dependent)

Results have shown that chromium supplementation appears to be more effective in patients with type 2 diabetes than in those with type 1 (Ravina & Slezack 1993).

Patients with early-stage type 2 diabetes of less than 2 years' duration were found to have lower chromium plasma levels (33%) and increased chromium excretion (100%) compared with healthy controls. Over a period of time this may contribute to the development of the insulin resistance seen in these patients (Morris et al 1999). Results of some trials suggest that improvements are dose-related but may also be affected by treatment duration, initial chromium status (Ghosh et al 2002, Amato et al 2000) and age. A controlled trial of elderly patients with diabetes (average age 73 years) reported that supplementation with chromium (200 μg twice daily) for 3 weeks improved fasting blood glucose, HbA_{1c}, and total cholesterol levels (Rabinovitz et al 2004), suggesting lower doses may be effective in older patients.

The most promising RCT to date tested chromium picolinate at doses of 200 and 1000 μg/day in subjects with type 2 diabetes who were instructed to maintain their current medications, diet and lifestyle habits. HbA_{1c} values (a marker of long-term

glycaemic control) improved significantly in the higher treatment group after 2 months and in both groups after 4 months' treatment. Fasting glucose was lower in the 1000 μg group after 2 and 4 months (4-month values: 7.1 ± 0.2 mmol/L vs placebo 8.8 ± 0.3 mmol/L). Two-hour glucose values were also significantly lower in the 1000 μg group after both 2 and 4 months (4-month values: 10.5 ± 0.2 mmol/L vs placebo 12.3 ± 0.4 mmol/L). Fasting and 2-hour insulin values decreased significantly in both groups receiving supplemental chromium after 2 and 4 months. Plasma total cholesterol also decreased in the subjects receiving 1000 μg chromium after 4 months (Anderson et al 1997). In people with type 2 diabetes taking sulfonylurea agents, chromium picolinate supplementation (equivalent to 1000 μg chromium) for 6 months significantly improved insulin sensitivity and glucose control; and attenuated bodyweight gain and visceral fat accumulation compared with placebo (Martin et al 2006).

Studies using chromium nicotinic acid have proven more promising with higher doses of nicotinic acid (100 mg/day) (Urberg & Zemel 1987) than those with low-dose nicotinic acid (1.8 mg) (Thomas & Gropper 1996), demonstrating a synergistic effect with chromium (200 μg/day).

Type 1 diabetes mellitus (insulin-dependent)

As chromium appears to improve insulin sensitivity rather than secretion its use in type 1 diabetes is probably limited (Edmondson 2002). One study did show reduced requirements for medication in 33.6% of patients with type 1 diabetes taking 200 μg chromium/day (Ravina & Slezack 1993), and another showed a 30% reduction in insulin requirements in 71% of subjects at the same dose (Ravina et al 1995), but as yet it is unclear which patients might respond to treatment.

Gestational diabetes

Pregnancy can be described as an increased insulin resistance state, which may result in gestational diabetes if the pancreas is unable to increase insulin levels to maintain blood glucose balance (Jovanovic & Peterson 1996). As such, the beneficial effect of chromium on insulin sensitivity provides a theoretical basis for its use in this condition. A small placebo-controlled trial using 4 or 8 μg/kg of chromium daily in gestational diabetes found a significant dose-dependent improvement in fasting insulin, 1-hour insulin and glucose, and postprandial glucose levels after 8 weeks' supplementation (Jovanovic et al 1999).

Corticosteroid-induced diabetes mellitus

Human trials have shown that corticosteroid use significantly increases urinary chromium excretion. Supplementation with chromium picolinate (equivalent to 600 μg chromium/day) in patients experiencing steroid-induced diabetes resulted in decreased fasting blood glucose values (from > 13.9 mmol/L to < 8.3 mmol/L). Furthermore, hypoglycaemic medications were also reduced by 50% in all patients within 1 week (Ravina et al 1999).

Prevention of long-term diabetic complications

Both QTc interval prolongation and chronic hyperinsulinaemia have been associated with atherosclerosis progression and increased cardiovascular morbidity in patients with type 2 diabetes. In a crossover trial of 60 subjects, chromium picolinate (1000 μg/day) for 3 months was shown to reduce both QTc interval duration and plasma insulin levels (Vrtovec et al 2005), probably by reducing the adrenergic activation of the sympathetic nervous system due to hyperinsulinaemia. Benefits were most significant in obese patients with higher peripheral insulin resistance (Vrtovec et al 2005).

Animal studies have found that chromium supplementation in mice with type 2 diabetes reduces the symptoms of hyperglycaemia and improves the renal function by recovering renal chromium concentration (Mita et al 2005, Mozaffari et al 2005) which may hold promise for human trials investigating the potential role of chromium in reducing the incidence of diabetic nephropathy.

Hypoglycaemia

Eight patients with reactive hypoglycaemia were given chromium chloride (equivalent to 200 μg chromium) for 3 months in a double-blind crossover study. Chromium supplementation significantly improved blood sugar regulation, insulin binding to receptors and red blood cells, and alleviated symptoms of hypoglycaemia (Anderson et al 1987).

A double-blind crossover study using chromium chloride (equivalent to 200 μg/day elemental chromium) for 8 weeks found a significant improvement in glycaemic control in subgroups where the 2-hour glucose level was > 10% above or below the fasting level (Bahijri 2000). In these subgroups chromium supplementation resulted in a 2-hour mean not significantly different to the fasting mean, suggesting an amphoteric effect on glycaemic control.

Hyperlipidaemia

It has been suggested that some of the potential benefits of HRT on total and LDL-cholesterol and total:HDL-cholesterol ratio may be related to its ability to improve chromium status (Bureau et al 2002, Roussel et al 2002) and trials yielding both positive and negative results for supplemental chromium in hyperlipidaemia have been reported. In a recent systematic review of 41 trials, eighteen studies, with a total 655 participants, reported lipid data for participants with either type 2 diabetes or glucose intolerance (Balk 2007). Overall, chromium supplementation was not found to exert a statistically significant effect on lipid levels in either group, although brewer's yeast supplementation did result in a statistically significant increase in HDL cholesterol (+0.21 mmol/L) compared to chromium picolinate.

Currently, it is unclear what circumstances or conditions and type of subjects are most likely to respond to treatment, so in practice a treatment trial period is often used to establish usefulness in individual patients.

A placebo-controlled trial using chromium tripicolinate (equivalent to 200 μg chromium/day) for

42 days found a reduction in total cholesterol, LDL and apolipoprotein B (the major protein of the LDL fraction) with a slight increase in HDL and a significant increase in apolipoprotein A1 (the major protein of the HDL fraction) (Press et al 1990). Another RCT of 40 hypercholesterolaemic subjects found that chromium polynicotinate (equivalent to 200 μg elemental chromium) twice daily for 2 months decreased total (10%) cholesterol and LDL-cholesterol (14%) (Preuss et al 2000).

A prospective, double-blind, placebo-controlled crossover study was performed with 30 subjects with type 2 diabetes. Triglyceride levels were significantly reduced (17.4%) and HDL levels increased during the 2 months' chromium picolinate supplementation (Lee & Reasner 1994). This is further supported by other trials (Bahijri 2000).

Another double-blind, placebo-controlled randomised study of young, non-obese adults taking chromium nicotinate (equivalent to 220 μg elemental chromium) for 90 days found no statistically significant differences in lipid levels (total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides) at this dose (Wilson & Gondy 1995). Similar results were found in older, non-obese subjects taking 1000 μg chromium picolinate for 8 weeks (Amato et al 2000) suggesting that subjects without identified pre-existing hypercholesterolaemia or other conditions predisposing them to hypercholesterolaemia may not respond to treatment. However, a prospective, double-blind, placebo-controlled crossover study of mostly hispanic patients with type 2 diabetes also elicited disappointing results, finding that only triglyceride levels were significantly reduced (17.4%) (Lee & Reasner 1994).

Obesity

As chromium has a role in maintaining carbohydrate and lipid metabolism, and potentiating insulin action, it has been suggested that chromium supplementation may have effects on body composition, including reducing fat mass and increasing lean body mass (Vincent 2003).

A meta-analysis of RCTs concluded that chromium picolinate elicited a relatively small effect compared with placebo for reducing body weight (Pittler et al 2003). One study, however, did show promising results using 200 μg niacin-bound chromium three times daily (total 600 μg/day) with moderate exercise. At these high doses, while overall reduction in body weight was similar for both the chromium and the placebo groups, total fat loss was more significant in the chromium group, suggesting a muscle sparing effect (Crawford et al 1999). A more recent RCT using chromium picolinate (equivalent to 200 μg chromium/day) for 12 weeks was unable to reproduce these effects (Lukaski et al 2007). Differences in form and dose may help to explain these contradictory results.

Atypical depression

In animal studies of chromium picolinate (8 μg/mL in drinking water) antidepressant effects have been reported (Khanam and Pillai 2006). In humans a small placebo-controlled double-blind study of chromium picolinate (600 μg/day) for 8 weeks was conducted in 15 patients with DSM-IV major depressive disorder, atypical type. Seven (70%) of 10 patients receiving chromium picolinate and none of the placebo group responded to treatment. Six subjects in the chromium group also experienced remission compared with none in the placebo group. However, a significant difference was not detected in the Hamilton Depression Scale at the end of treatment (Chromium, atypical depression 2003, Davidson et al 2003). As depression is a common comorbidity in diabetes, further investigation is warranted.

OTHER USES

While controlled trials are yet to be conducted or are inconclusive in some cases, chromium is also used in the following conditions, based on a theoretical understanding of its pharmacological actions.

Exercise aid

Chromium has demonstrated an ability to enhance insulin-mediated glucose uptake in cultured cells, however supplementation in humans does not appear to exert such benefits. In a small RCT, 16 overweight men were randomised to receive chromium picolinate (equivalent to 600 μg chromium/day) for 4 weeks before being subjected to supramaximal cycling exercises to deplete glycogen stores, followed by high glycaemic index carbohydrate feedings. At this dose, supplementation did not appear to improve glycogen synthesis during the recovery phase (Volek et al 2006).

In addition studies in female athletes have shown no effect on body composition or muscle strength following supplementation with 500 μg chromium picolinate daily during 6 weeks of resistance training (Livolsi et al 2001). In a clinical trial of older women a high-dose chromium picolinate supplement did not affect body composition, skeletal muscle size or maximal strength above that of resistance training alone (Campbell et al 2002). A meta-analysis of trials of dietary supplements for enhancing lean muscle mass and strength during resistance training did not support the use of chromium for this purpose (Nissen & Sharp 2002).

Polycystic ovarian syndrome

The relationship between PCOS and insulin resistance provides a theoretical basis for the use of chromium in this condition. A small study has found that chromium picolinate (200 μg/day) appears to improve glucose tolerance but not ovulatory frequency in women with polycystic ovary syndrome (Lucidi et al 2005). Larger studies are required to investigate the potential benefits of chromium supplementation in this population.

Syndrome X

Syndrome X highlights the link between insulin resistance and lipid profiles. As a number of studies have proved promising in regard to both these factors, a theoretical basis exists for the use of chromium in this condition. Furthermore, the

presence or absence of this syndrome may explain why studies have shown varying responses to treatment with chromium in the past and may provide direction for more consistent trial results in future studies.

Prevention of myocardial infarction

In a population-based case–control study, toenail chromium concentration was inversely associated with the risk of a first myocardial infarction in men. Men with the highest levels of chromium were 35% less likely to have a heart attack than those with the lowest levels (Guallar et al 2005). Future studies are required to determine whether chromium supplementation may be beneficial for the prevention of cardiovascular incidents.

Osteoporosis

Effects on bone resorption, calcium excretion and collagen production suggest a role in the prevention of osteoporosis (Evans et al 1995, McCarty 1995); however, there are no controlled trials to determine clinical effectiveness.

DOSAGE RANGE

The ESADDI is 50–200 μg/day. The most common doses studied include 200, 400, 600 and 1000 μg daily. Doses in the upper range appear to produce more convincing trial results.

Australian adequate intake

- Women: 25 μg/day.
- Men: 35 μg/day.

Chromium picolinate is the best absorbed form, although chromium nicotinate may have a better safety profile and the synergistic effects with nicotinic acid may have further benefits in some conditions, especially with regard to lipid profiles.

ADVERSE REACTIONS

It is important to differentiate between hexavalent chromium (Cr IV) and trivalent chromium (Cr III) when assessing toxicity. Cr IV is used in industry and is highly toxic, whereas Cr III is approved for use as a supplement and does not attract the same concerns. Recent in vitro studies suggest a possibility that Cr III may oxidise to Cr V, a potential carcinogen (Shrivastava et al 2005); however, this requires confirmation from in vivo studies.

Irritability and insomnia have been reported with chromium yeast supplementation (Schrauzer et al 1992).

A follow-up survey of the Anderson trial at 1 year found no side effects for doses up to 1000 μg/day of chromium picolinate (Cheng et al 1999).

Of five anecdotal adverse reports attributed to chromium picolinate and reviewed by Lamson and Plaza (2002), only one reporting transient and vague symptoms was considered to be a possible adverse reaction (Huszonek 1993). Three could not be validated by the reviewers due to concurrent medications (Cerulli et al 1998, Martin & Fuller 1998, Wasser et al 1997), and another involved the inappropriate use of potassium dichromate, a strong oxidising agent known to elicit reactions in a majority of people (Fowler 2000). A case report exists of toxic hepatitis and greatly elevated hepatic chromium levels (>10-fold normal) after 5 months' ingestion of chromium polynicotinate in combination with vegetable extracts (Lanca et al 2002). Whether chromium supplementation was responsible for this incident is currently unclear.

Clinical note — Does chromium picolinate cause cancer?

There has been some concern in the past arising from in vitro studies suggesting chromium picolinate exerts clastogenic effects in hamster ovary cells (Stearns et al 1995a, 2002) and possible DNA damage (Levina & Lay 2008, Speetjens et al 1999). This has been refuted by a number of authors, suggesting the doses tested were several thousand times higher than equivalent human doses (McCarty 1997, Salmon 1996) and that chromium is relatively short lived so that the accumulated doses suggested by researchers (Stearns et al 1995a) were not feasible (Hepburn & Vincent 2003). Furthermore in vivo evidence from animals and humans suggests that under normal circumstances trivalent chromium (Cr III) has only restricted access to cells, which would limit or prevent genotoxic effects. Therefore supplementation at moderate doses is not currently considered to be detrimental (Eastmond et al 2008). It should also be noted that picolinic acid appears to be the source of the concern and other forms of chromium have not been implicated (Bagchi et al 2002, Stearns et al 1995b).

No adverse effects on iron status

As chromium competes with iron for binding to transferrin it has been suggested that high-dose chromium supplementation may adversely affect iron status. While some studies support this (Ani & Moshtaghie 1992), others show that serum iron concentrations and serum ferritin concentrations are unaffected by chromium picolinate supplementation (Campbell et al 1997, Lukaski et al 2007). It would appear that iron does not use all available transferrin and therefore this situation is unlikely under normal conditions.

SIGNIFICANT INTERACTIONS

Corticosteroids

Corticosteroids increase urinary losses of chromium, and chromium supplementation has been shown to aid in recovery from steroid-induced diabetes mellitus. Therefore a beneficial interaction may be possible (Kim et al 2002).

Hypoglycaemic medicines

Chromium may reduce requirements for hypoglycaemic agents (Ravina & Slezack 1993, Ravina et al 1995). While a beneficial interaction is possible, this combination should be used with caution and drug

requirements monitored and adjusted if necessary by a healthcare professional.

Hormone replacement therapy

Women receiving HRT appear to have improved chromium status (Bureau et al 2002, Roussel et al 2002) and the addition of trivalent chromium to 17-beta-oestradiol may enhance IL-6 inhibition in experimental models (Jain et al 2004). Whether this alters chromium requirements is unknown.

Lipid-lowering medicines

Additive effects are theoretically possible as some clinical studies have indicated lipid-lowering effects. Observe patients taking this combination and monitor drug requirements.

CONTRAINDICATIONS AND PRECAUTIONS

Hypersensitivity to chromium.

PREGNANCY USE

Oral ingestion of doses typically found in the diet are likely to be safe. Taken under professional supervision, supplements are also likely to be safe and may be beneficial in the prevention and treatment of gestational diabetes (Jovanovic & Peterson 1996, Jovanovic et al 1999).

PRACTICE POINTS/PATIENT COUNSELLING

- Chromium is an essential trace mineral required for carbohydrate, lipid, protein and corticosteroid metabolism.
- Dietary intakes are generally below the minimum suggested safe and adequate levels, and factors such as high-sugar diets, corticosteroid use, excessive exercise, infection, physical trauma and psychological stress further increase the risk of deficiency.
- Chromium supplements are used in the treatment of type 2 diabetes, hypoglycaemia, gestational diabetes and hyperlipidaemia. However, inconsistent results have been obtained from clinical studies.
- It is also used in the treatment of obesity, atypical depression, syndrome X, PCOS and osteoporosis, and in resistance training.
- Supplemental forms used in trials include organic chromium complexes, such as chromium picolinate and chromium nicotinate, and inorganic salts such as chromium chloride.

PATIENTS' FAQs

What will this supplement do for me?

Chromium is essential for health and wellbeing. It may also have beneficial effects in type 2 diabetes, gestational diabetes, hypoglycaemia and elevated cholesterol and triglyceride levels in some people, although scientific research has produced mixed results.

When will it start to work?

Effects in diabetes and elevated cholesterol or triglyceride levels require 8–12 weeks to establish.

Are there any safety issues?

Used under professional supervision, chromium supplements are considered safe.

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Cinnamon

HISTORICAL NOTE Cinnamon has been used since ancient times for a variety of uses and was considered a precious commodity. In ancient Egypt, it was used as a flavouring for beverages, in combination with other spices for embalming, and as a medicinal agent. Ancient Chinese herbals mention it as a medicinal treatment as early as 2700 BC (Castleman 1991) and it has long been used as a remedy for diabetes in China, Korea, Russia and India. In medieval Europe, cinnamon was a common ingredient in cooking, often used together with ginger. Due to the high demand for cinnamon, discovering lands where it grew was a primary motive for a number of explorers' enterprises in the 15th and 16th centuries. Today, two main types of cinnamon are cultivated, *Cinnamomum verum*, also known as Ceylon cinnamon, and *Cinnamomum cassia*, also known as Chinese cinnamon.

OTHER NAMES

Cinnamomum verum: cannelle de ceylan, Ceylon celonzimi cinnamon, Ceylon cinnamon, cinnamon bark, cortex cinnamomi ceylanici, dalchini, ecorce de cannelier de Ceylan, echter, gujerati-dalchini, kannel, kuei-pi, kurundu, kulit kayumanis, ob choei, tamalpatra, wild cinnamon

Cinnamomum cassia Blume: cassia, Chinese cinnamon, dalchini, guipi, kannan keihi, keishi, lavanga-pattai, lurundu, macrophyllos cassia bark tree, rou gui, Saigon cinnamon, saleekha, taj, toko keihi, Viet Nam cinnamon

BOTANICAL NAME/FAMILY

Cinnamomum verum J.S. Presl (also known as *C. zeylanicum* Nees) and *C. cassia* Blume (family Lauraceae)

PLANT PARTS USED

Dried inner bark of the shoots grown on cut stock of *C. verum* or of the trunk bark, freed from the underlying parenchyma; outer cork of *C. cassia* Blume.

CHEMICAL COMPONENTS

Both forms of cinnamon contain an essential oil that consists primarily of cinnamaldehyde (up to 80% in *C. verum* and 90% in *C. cassia*) and differ primarily in their eugenol and coumarin content. The volatile oil from *C. verum* contains 10% eugenol whereas the oil from *C. cassia* contains only trace amounts. Also, *C. cassia* contains coumarin, which is not found substantially in *C. verum*. The bark of *C. verum* contains caryophyllene, cinnamyl acetate and linalool whereas the bark of *C. cassia* contains catechin and 1,8 cineole.

MAIN ACTIONS

The cinnamaldehyde constituent in cinnamon is attributed with producing most of the herb's biological effects. This component is found in large amounts in both forms of cinnamon. More recently, several other constituents have also been tested in isolation and found to exert significant pharmacological effects.

Antibacterial and fungicidal effects

Several in vitro studies have identified broad-spectrum antibacterial and fungicidal effects for both forms of cinnamon. This has been chiefly attributed to cinnamaldehyde although other constituents such as eugenol, carophyllene and 1,8 cineole also exhibit antimicrobial properties.

C. verum demonstrated activity against a wide range of bacteria and fungi including *Bacillus subtilis*, *Escherichia coli*, *Saccharomyces cerevisiae*, *Candida albicans*, *Listeria monocytogenes* and *Salmonella enterica* (De et al 1999, Friedman et al 2002, Matan et al 2006, Simic et al 2004, Tampieri et al 2005).

C. cassia extracts significantly inhibited *Helicobacter pylori* in vitro and produced zones of inhibition greater than or equal to commonly used antibiotics (Tabak et al 1999). The essential oil of *C. cassia* also exhibited strong antifungal properties in vitro (Giordani et al 2006). When tested

with amphotericin, a reduced amount of drug was required for adequate antifungal effects.

Antibacterial activity for the oil has also been demonstrated against antibiotic-resistant *E. coli* and *Staphylococcus aureus* (Friedman et al 2004).

Fungi in bakery products

Antifungal activity against the more common fungi causing spoilage of bakery products, *Eurotium amstelodami*, *E. herbariorum*, *E. repens*, *E. rubrum*, *Aspergillus flavus*, *A. niger* and *Penicillium corylophilum*, was demonstrated for cinnamon oil in vitro (Guynot et al 2003).

Respiratory tract pathogens

An in vitro study of the antibacterial activity of essential oils and their major components against the major bacteria causing respiratory tract infection indicated that cinnamon bark oil was effective against *Haemophilus influenzae*, *Streptococcus pneumoniae* and *S. pyogenes* (Inouye et al 2001).

Oral pathogens

According to in vitro research, cinnamon bark oil is an effective inhibitor of bacteria causing dental caries and periodontal disease (Saeki et al 1989).

Carminative

The essential oil exhibits carminative activity and decreases smooth muscle contractions in guinea-pig trachea and ileum, and in dog ileum, colon and stomach (WHO 2004). The oil has also demonstrated antifoaming activity in a foam generator model for flatulence (ESCOP 2003). The active antispasmodic constituent is considered to be cinnamaldehyde.

Hypoglycaemic activity

Using an experimental model of diabetes, Kim et al observed that cinnamon extract significantly reduced blood glucose levels after two weeks of treatment (Kim et al 2006). A significant decrease in total cholesterol levels and triglycerides and increase in HDL-cholesterol was also found for cinnamon-treated mice.

Enhanced insulin sensitivity

Water soluble compounds extracted from *C. cassia* potentiate insulin activity, as measured by glucose oxidation in the rat epididymal fat-cell assay. The most active compound, methylhydroxy chalcone polymer (MHCP), increased glucose metabolism approximately 20-fold and was an effective mimetic of insulin according to an in vitro study. When combined with insulin, the responses were greater than additive, indicating synergism between the two compounds (Jarvill-Taylor et al 2001). According to Anderson et al (2004), MHCP is actually a water-soluble polyphenolic type-A polymer that increases insulin sensitivity by activating the key enzymes that stimulate insulin receptors, while inhibiting the enzymes that deactivate them. More specifically, extracts of cinnamon activate insulin receptor kinase and inhibit dephosphorylation of the insulin receptor, leading to maximal phosphorylation of the insulin receptor.

The United States Agricultural Research Service has filed a patent application on the active substances.

Antitumour activity

Cinnamon extract displayed anti-tumour activity when administered orally or by intra-tumour injection (Kwon et al 2009). It strongly inhibited the expression of pro-angiogenic factors and master regulators of tumour progression. The effects were seen not only in melanoma cell lines but also in an experimental melanoma model. In addition, cinnamon extract treatment increased the anti-tumour activities of $CD8^+$ T cells by increasing the levels of cytolytic molecules and their cytotoxic activity. These findings are important as tumour cells recruit new blood vessels by excessive production of pro-angiogenic factors that play a pivotal role in tumour progression and tumour survival.

Anti-inflammatory and antioxidant

Potent antioxidant and anti-inflammatory activity for cinnamon bark oil has been demonstrated in vitro and for the dry ethanolic extract in vivo (ESCOP 2003, Jarvill-Taylor et al 2001, Lee et al 2003, Mathew & Abraham 2006).

OTHER ACTIONS

A dose-dependent antinociceptive activity has been demonstrated for *Cinnamomum zeylanicum* when administered orally to mice in the hot plate and acetic acid writhing induced tests (Atta and Alkofahi 1998).

C. cassia also possesses antipyretic activity (Kurokawa et al 1998) and reduced the occurrence of ulcers in rats in a dose-dependent manner in a study that administered an aqueous extract (Tanaka et al 1989).

Besides antispasmodic and broad-spectrum antibacterial and fungicidal activities, cinnamaldehyde exhibits antitumour effects (Kwon et al 1998) and cytotoxicity (Moon & Pack 1983).

CLINICAL USE

Cinnamon has been used as a medicinal agent in several traditional healing systems. In the last two decades, scientific investigation has been undertaken to investigate its clinical effects. Evidence to support its clinical use is still mainly derived from in vitro and in vivo research, and from traditional usage, however an increasing number of clinical trials are now being published.

Dyspepsia and related symptoms

Cinnamon bark oil and crushed cinnamon bark is used in the treatment of dyspeptic conditions, such as mild spastic conditions of the gastrointestinal tract, fullness and flatulence, loss of appetite and diarrhoea. Although controlled studies are unavailable, evidence of antispasmodic and antifoaming activity in animal models and a long tradition of use provide some support for its use in these indications.

Cinnamon bark and Chinese cinnamon are approved by the German Commission E for the

treatment of loss of appetite and dyspeptic complaints such as mild gastrointestinal spasms, bloating and flatulence (Blumenthal et al 1998).

Helicobacter pylori infection

According to a placebo-controlled study of 15 volunteers with documented *H. pylori* infection, an ethanolic extract of cinnamon was ineffective at eradicating the infection when used at a dose of 40 mg twice daily for 4 weeks (Nir et al 2000). Considering this is an extremely low dose, further investigation is required using therapeutic doses in order to adequately test its effectiveness for this indication.

Diabetes

Cinnamon has a long history of use for diabetes in China, India, Korea and Russia. To date, four clinical studies have investigated its effects in this population, producing mixed results.

In 2003, a randomised, placebo-controlled study of type 2 diabetes demonstrated that cinnamon exerts clinically significant glucose- and lipid-lowering effects (Khan et al 2003). The study involved 60 people who were divided into six groups. Groups 1–3 consumed 1, 3 or 6 g of cinnamon daily whereas groups 4–6 were given the equivalent number of placebo capsules and acted as controls. The volunteers were not using insulin therapy and had a fasting blood glucose reading between 140 and 400 mg/dL. After 40 days of treatment, all three doses of cinnamon reduced mean fasting serum glucose by 18 to 29%, triglycerides by 23 to 30%, LDL-cholesterol by 7 to 27%, and total cholesterol by 12 to 26%. No significant changes were observed in the placebo groups. The effect on glucose and lipid levels was sustained 20 days after treatment had ceased, suggesting that cinnamon would not need to be consumed every day. The cinnamon used was *C. cassia*, which was finely ground and put into capsules.

More recently, a 6-week placebo-controlled study was conducted in 25 postmenopausal women with type 2 diabetes and produced different results (Vanschoonbeek et al 2006). Researchers assessed the effects of cinnamon supplementation (*C. cassia*, 1.5 g/day) on fasting blood glucose, insulin and glycosylated haemoglobin concentrations, indices of oral glucose tolerance and whole-body insulin sensitivity, and fasting blood lipid profiles. During the trial, volunteers maintained their normal dietary and physical activities and continued all medication. After 6 weeks, cinnamon supplementation had no significant effect on fasting plasma glucose or insulin concentrations, whole-body oral glucose tolerance, or blood lipid profiles in this sample.

It is not clear why positive results should be observed in the first study and not in the second. The dose of cinnamon used was within the range expected to be active and the same form was used. Vanschoonbeek et al report that baseline values of fasting glucose and triglycerides were different for subjects participating in the two studies and discrepant results may be accounted for by this difference and by a lack of nutritional standardisation in the study by Khan et al.

Most recently, a crossover study of 15 healthy volunteers reported that ingestion of 3 g cinnamon significantly reduced postprandial serum insulin and increased glucagon-like peptide-1 concentrations without significantly affecting blood glucose, glucose-dependent insulinotropic polypeptide, the ghrelin concentration, satiety, or gastric emptying rate. A lower dose of cinnamon (1 g) was also tested and found to have no effects on any measurements (Hlebowicz et al 2009).

Gestational diabetes

A randomised, double-blind placebo controlled study of 51 women with gestational diabetes found that 6 weeks of treatment with 1 g of cinnamon daily produced a trend towards decreased insulin requirements (53.85% cinnamon vs 44% placebo, $P = 0.58$); however, this did not reach significance (Graham et al 2005). The cinnamon used was *C. cassia*. The researchers suggested that a longer duration of treatment may be required to produce better results.

Metabolic syndrome

A water-soluble extract of cinnamon (Cinnulin PF(R) 500 mg/day) significantly reduced fasting blood glucose, systolic blood pressure and increased lean body mass according to a placebo controlled trial of 22 subjects with prediabetes and metabolic syndrome (Ziegenfuss et al 2006). The study was conducted over 12 weeks and also detected small but statistically significant decreases in body fat in the cinnamon treated group when within-group analyses were performed.

Polycystic ovarian syndrome

A pilot study involving 15 non-diabetic women with oligomenorrhoea or amenorrhoea and polycystic ovaries which compared cinnamon (333 mg cinnamon extract taken three times a day) to placebo (Wang et al 2007). The randomised study found oral cinnamon extract resulted in a significant reduction in fasting glucose as well as insulin resistance, as measured by various indices of insulin sensitivity from fasting and oral glucose tolerance test (OGTT) values. Specifically, fasting glucose was reduced by 17% during the 8-week treatment period. The reduction in insulin resistance appears to be mediated through an increase in glucose utilisation, as there were no significant alterations in hyperinsulinaemia measured by fasting insulin or mean insulin levels during OGTT. These preliminary findings are consistent with prior in vivo animal and human studies.

OTHER USES

Traditional uses

Cinnamon has been used traditionally by ancient healers from many backgrounds for stomach cramps, flatulence, nausea, vomiting, diarrhoea, infant colic, common infections and also female reproductive problems such as dysmenorrhoea,

menorrhagia, lactation and pain in childbirth. It has also been used as an ingredient in topical preparations for pain and inflammation. Cinnamon is often used in combination with other herbs and spices for most of these indications. In TCM it is considered to warm the kidneys and fortify yang, so is used for impotence among other indications. In Ayurvedic medicine and in China, Korea and Russia it has long been used as a treatment for diabetes.

Natural food preservative

Spices such as cinnamon have been used traditionally for the preservation of food products. The considerable antimicrobial, fungicidal and antioxidant properties of cinnamon provide a theoretical basis for its use.

DOSAGE RANGE

General guide

- Dried bark (crushed cinnamon): 1.5–4 g taken up to four times daily.
- Fluid extract 1:1: 0.5–1.0 mL taken up to three times daily.
- Tea: half to three-quarters teaspoon of powdered cinnamon in a cup of boiling water taken 2–3 times daily with meals.
- Essential oil: 0.05–0.2 mL diluted in carrier oil.

According to clinical studies

Diabetes

- 3–6 g daily of powdered cinnamon (*C. cassia*) administered in capsules.

Loss of appetite or digestive complaints

- Essential oil: 0.05–0.2 g daily.
- Fluid extract (1:1 g/mL): 0.7–1.3 mL three times daily.
- Infusion or decoction: 0.7–1.3 g in 150 mL water three times daily.
- Tea: 1–4.5 g daily using *C. cassia* bark.

TOXICITY

The oral LD_{50} for cinnamon bark oil in rats is 4.16 g/kg and 3.4 mL/kg body weight.

ADVERSE REACTIONS

When the powdered herb is ingested orally, it is generally well tolerated; however, when cinnamon oil is applied topically, allergic reactions are possible as cinnamaldehyde may cause allergic contact dermatitis (Cheung et al 2003).

SIGNIFICANT INTERACTIONS

Controlled studies are not available, therefore interactions are based on pharmacological activity and are largely theoretical and speculative.

Hypoglycaemic agents

Oral ingestion of cinnamon capsules may reduce blood glucose levels, therefore theoretically, an additive effect is possible with concurrent use — observe; potential beneficial interaction under professional supervision.

CONTRAINDICATIONS AND PRECAUTIONS

Cinnamon is contraindicated in people with an allergy to cinnamon or Peru balsam, in cases of fever of unknown origin, active stomach or duodenal ulcers (WHO 2004).

PREGNANCY USE

C. cassia or *C. zeylanicum/verum* should not be used in pregnancy; however, usual dietary intakes are likely to be safe. Currently, evidence of teratogenicity from animal studies is contradictory.

PRACTICE POINTS/PATIENT COUNSELLING

- Cinnamon has been used since ancient times as a flavouring and medicinal agent.
- It is a natural food preservative with antioxidant and wide ranging antimicrobial and antifungal properties.
- It has been used traditionally to treat dyspepsia, nausea, flatulence, poor appetite, stomach cramps and diarrhoea. Some evidence suggests it may be effective for some of these indications.
- Whether ground cinnamon (*C. cassia*) reduces blood glucose and lipid levels and can be useful for people with type 2 diabetes is uncertain as clinical studies have produced mixed results
- Cinnamon oil can cause allergic contact dermatitis when used topically and should be avoided by people with allergies to cinnamon or Peru balsam, pregnant women or those with active gastrointestinal ulcers.

PATIENTS' FAQs

What will this herb do for me?

Cinnamon is a natural food preservative with wide ranging antimicrobial and antifungal properties. It may improve digestion and ease symptoms of dyspepsia, flatulence and nausea. It may also lower blood glucose, total cholesterol and triglyceride levels, however more research is required to confirm these effects.

When will it start to work?

The effects on digestion should start rapidly; however, effects on blood glucose and lipid levels may take 1 month or more.

Are there any safety issues?

Cinnamon oil can cause allergic contact dermatitis when used topically and should be avoided by people with allergies to cinnamon or Peru balsam, pregnant women or those with active gastrointestinal ulcers.

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Cloves

HISTORICAL NOTE Spices such as cloves have been used as food preservatives, disinfectants and antiseptics for centuries (De et al 1999). Modern research has confirmed that cloves are an effective preservative that inhibit the growth of many food-poisoning and food-spoiling bacteria.

COMMON NAME
Cloves

OTHER NAMES
Oil of cloves, Oleum caryophylli, *Eugenia caryophyllata*, *Eugenia aromatica*, *Caryophyllus aromaticus*, Myrtaceae

SCIENTIFIC NAME
Syzygium aromaticum (family Myrtaceae)

PLANT PART USED
Dried flower buds (clove oil is distilled from this plant part).

CHEMICAL COMPONENTS
The main constituent of clove oil is eugenol. Other components include beta-caryophyllene, acetyl eugenol, isoeugenol, eugenine, kaemferol, tannins, gallic acid, vitamin C, minerals (boron, calcium, chromium, iron, manganese, magnesium, potassium, phosphorus), flavonoids (Nassar 2006).

MAIN ACTIONS
Because of cloves' significant eugenol content, most pharmacological activity is based on studies involving eugenol.

Local analgesic, local anaesthetic and anti-inflammatory
The local analgesic and anti-inflammatory activity of clove oil is mainly due to the eugenol component. Eugenol acts on contact to depress nociceptors, the sensory receptors involved in pain perception (Brodin & Roed 1984). Eugenol also inhibits prostaglandin biosynthesis through potent cyclo-oxygenase-1 and -2 inhibitory activity (Huss et al 2002, Kelm et al 2000) and modulates inflammatory pathways by inhibiting

the release of leukotrienes (Raghavenra et al 2006). According to experiments with an animal model, daily doses of eugenol produce a cumulative effect after 5 days of continuous administration, producing a statistically significant reduction in neuropathic pain (Guénette et al 2007). Although eugenol is chiefly responsible for much of the pharmacological activity of cloves, other constituents are also involved (Ghelardini et al 2001a).

Beta-caryophyllene is another key component of clove oil, which exhibits significant anti-inflammatory and rapid local anaesthetic activity in several animal models (Ghelardini et al 2001b, Muruganandan et al 2001). Local anaesthetic effects develop within 5 minutes of application and diminish after about 15 minutes.

Antiseptic — fungicidal, antibacterial, antiviral, antiparasitic

Clove oil has an inhibitory effect against yeasts and fungi in vitro (Arora & Kaur 1999). Cloves are effective against species belonging to the *Eurotium*, *Aspergillus* and *Penicillium* genera in vitro (Guynot et al 2003) and clove essential oil has exhibited strong antifungal activity against *Aspergillus* and aflatoxigenic strains (Bluma et al 2008, Viuda-Martos et al 2007) and various other fungal species (Park et al 2007).

Experiments with animal models have identified significant activity against *Candida albicans*. Vaginal candidiasis responded to treatment of topical application of clove oil in animal models suggesting that further investigation is warranted to determine clinical relevance (Ahmad et al 2005). Another animal experiment found that oral intake of cloves reduced *Candida albicans* growth in the alimentary tract (Taguchi et al 2005). It is likely that the eugenol component is important for such effects, as in vitro experiments identified that eugenol displays anticandidal activity by affecting the envelope of the organism (Braga et al 2007, Fu et al 2007).

Antibacterial activity has also been demonstrated for cloves and several of its key constituents. Cloves has activity against gram-negative, anaerobic, periodontal oral pathogens, including *Porphyromonas gingivalis* and *Prevotella intermedia* (Cai & Wu 1996). Activity has also been demonstrated against *Bacillus subtilis*, *Listeria monocytogenes*, *Salmonella enterica*, *Escherichia coli* and *Saccharomyces cerevisiae* (Burt & Reinders 2003, Chami et al 2005, De et al 1999, Dorman & Deans 2000, Friedman et al 2002, Fu et al 2007) and *Staphylococcus epidermidis* (Fu et al 2007). Aqueous extract of cloves demonstrated a strong inhibitory action against six *Helicobacter pylori* strains in vitro (Yang et al 2005). Further research is required to determine the clinical relevance of these in vitro findings and establish whether cloves may be utilised as an effective treatment for common infections.

In vitro assays have identified inhibitory effects on hepatitis C virus protease (Hussein et al 2000) and human cytomegalovirus (Shiraki et al 1998, Yukawa et al 1996). An animal model confirmed significant activity against herpes simplex virus type 1 (Kurokawa et al 1998). An inhibitory effect against parasitic growth has been demonstrated in vitro for clove oil (Santoro et al 2007).

OTHER ACTIONS

Antihistamine

Clove bud extracts inhibit histamine release from mast cells in vivo and in vitro (Kim et al 1997, 1998, Shakila et al 1996).

Antioxidant

Several constituents within the flower have antioxidant activity, especially eugenol, which has been the focus of most antioxidant research (Duke 2002). Studies with cloves and eugenol have demonstrated protective effects against several agents, which cause damage to cells and tissues via an oxidative stress mechanism.

Cloves illustrated a protective effect against a cytotoxic agent (peroxynitrite) that causes damage to proteins, lipids and DNA (Ho et al 2008) and significantly reversed isoprenaline-induced cardiac hypertrophy in rats (Choudhary et al 2006). In other studies, eugenol was shown to reduce radiation-induced membrane damage (Pandey et al 2006), to prevent lipid peroxidation and increase glutathione (Kabuto et al 2007).

Antispasmodic

Both beta-caryophyllene and eugenol have antispasmodic activity (Duke 2002).

Antiplatelet

Eugenol inhibits platelet aggregation in vitro (Srivastava 1993, Srivastava & Malhotra 1991). It was more potent than aspirin in several experimental models and equivalent to indomethacin in one (Srivastava 1993).

Anticarcinogenic

Eugenol essential oil showed anticancer apoptosis activity on HL-60 human promyelocytic leukaemia cells in vitro (Yoo et al 2005). Further chemopreventive potential was explored in mice with induced lung carcinogenesis. A clove infusion, administered orally, was found to significantly reduce proliferating cells and increase apoptosis. The cloves down-regulated some growth-promoting proteins, while at the same time upregulating the expression of some pro-apoptotic proteins (Banerjee et al 2006). A later in vitro study confirmed apoptosis activity with eugenol (and its analogues) and suggested that it may have a chemotherapeutic role (Carrasco et al 2008). An aqueous infusion of cloves, administered orally, in a mouse experiment delayed the formation and reduced skin papilloma (Banerjee & Das 2005)

Antidiabetic

In vitro tests have identified hypoglycaemic activity for cloves. It appears that a phenolic compound in cloves may be the key constituent responsible and acts by repressing the expression of genes, which control hepatic gluconeogenesis (Prasad et al 2005). Commercially sold culinary cloves were also shown

to be potent inhibitors of fructose-mediated protein glycation and so may have antidiabetic potential (Dearlove et al 2008). Further research is required with in vivo models of diabetes to determine whether these effects may have clinical significance.

Cognitive effects

An animal study found that intraperitoneally administered clove extract (200 mg/kg) improved short-term memory recall but caused some impairment in learning ability (Morshedi et al 2006).

CLINICAL USE

The clinical effects of cloves and clove oil have not been significantly investigated; however, an understanding of the herb's pharmacological activity suggests a role in the treatment of several conditions.

Toothache and relief of dry socket pain

Clove oil and dried clove buds are used in dentistry to relieve dental pain and reduce infection. Based on the evidence available, Commission E has approved cloves for use as a local anaesthetic and antiseptic (Blumenthal et al 2000). In one study, clove oil was found to be as effective as benzocaine as a topical anaesthetic before needle insertion in dentistry (Alqareer et al 2006).

Oral hygiene

Used as an antiseptic and antibacterial agent for the oral mucosa, clove is used as an ingredient in mouth rinses and gargles. Its established antiseptic activity provides a theoretical basis for efficacy.

Herpes simplex virus type 1

One study using a combination of acyclovir and cloves administered orally found this to be superior to acyclovir alone in the treatment of herpes simplex virus type 1 infection (Kurokawa et al 1995). The combination significantly reduced the development of skin lesions and/or prolonged survival times of infected mice and reduced viral loads.

Headache (as part of a combination)

Tiger balm is a popular OTC preparation that contains clove oil, menthol, cassia oil, camphor, cajuput oil and sometimes peppermint oil. It is generally used to relieve the symptoms of sore muscles, but a randomised, double-blind study found that it is also as effective as paracetamol in reducing headache severity (Schattner & Randerson 1996). Although encouraging, the role of cloves in this combination is difficult to assess from the study.

Type 2 diabetes

In a small study, 36 people with type 2 diabetes were given 0, 1, 2 or 3 g capsules of cloves for 30 days. All the groups administered with cloves had significantly lowered serum glucose, triglycerides, total and LDL cholesterol and there was no change to HDL cholesterol. After 10 days washout period all these parameters were still significantly lower than at the start of the trial (Khan et al 2006). Further research is warranted to confirm clinical use for type 2 diabetes and to assess any side effects with oral ingestion of cloves.

OTHER USES

Cloves have been investigated as an agent to protect harvests from fungal contamination (Ranasinghe et al 2002).

DOSAGE RANGE

- Powder: 120–300 mg as a single dose.
- Oil: 0.05–0.2 mL as a single dose.
- Toothache or gum inflammation: oil of clove is applied directly to the site.
- Dry socket: the area is packed with dried flower buds steeped in oil.
- Headache: one drop of oil massaged into each temple or area of pain.

ADVERSE REACTIONS

According to one review, contact dermatitis has been reported, and local application may cause irritation to mucous membranes in sensitive individuals. Oral use of the oil can cause nervous system depression, seizures, hepatic dysfunction and irritation to mucosal tissues.

SIGNIFICANT INTERACTIONS

Cloves have been found in vitro to strongly inhibit metabolism mediated by CYP3A4 and CYP2D6. In vivo studies are currently under progress and clinical relevance has yet to be established (Usia et al 2006). If cloves are only used topically, these interactions are unlikely to be relevant.

CONTRAINDICATIONS AND PRECAUTIONS

None known.

PREGNANCY USE

Safety unknown.

PRACTICE POINTS

- Clove flower buds and clove oil has antiseptic, analgesic, anti-inflammatory and local anaesthetic properties.
- It is directly applied to relieve the symptoms of toothache and dry socket.
- Clove oil is also used in mouth rinses and gargles to improve oral hygiene.
- Massaging one drop of oil into the temples has been used to treat headache.
- This herb and its essential oil should not be taken internally.

PATIENTS' FAQs

What will this herb do for me?

Clove flower buds and clove oil have antiseptic, anti-inflammatory, analgesic and local anaesthetic properties that are useful in the treatment of toothache, dry socket and common mouth infections. Massaging one drop of the oil into the temples may relieve the symptoms of headache.

When will it start to work?

Research suggests that effects are almost immediate, although short lasting.

Are there any safety issues?

Clove buds and clove oil should not be taken internally, and only applied externally, although using cloves as a spice in cooking may give you some of the antioxidant benefits.

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Cocoa

HISTORICAL NOTE Cocoa originates from Mexico where the Mayas, Incas and Aztecs considered it the food of the gods. Chocolate, mixed with vanilla and sugar, was first introduced as a beverage in Europe by Columbus and was considered an aphrodisiac and a symbol of wealth and power. The phenolics in chocolate prevent the fat becoming rancid, decreasing the need for added preservatives. This quality was exploited during World War II when at times US troops were rationed three chocolate bars per day during heavy combat as their sole source of nourishment (Waterhouse et al 1996).

COMMON NAME

Chocolate, cocoa, cocoa liquor, cocoa mass, baking chocolate, Cocoapro™, Acticoa™

BOTANICAL NAME/FAMILY

Theobroma cacao (family Sterculiaceae)

PLANT PARTS USED

Cocoa is produced through a process of fermenting the seeds from the pods of the cacao tree, *Theobroma cacao*. The beans are dried, roasted and crushed to produce high-fat, unsweetened chocolate, which is also called baking chocolate. This intermediate is pressed and alkalised to form cocoa powder, which is then homogenised with sugar and cocoa butter, and sometimes milk, to ultimately form chocolate. Dark chocolate generally contains more than 50% cocoa, whereas mass-produced milk chocolate contains only around 10% cocoa. White chocolate is based on cocoa butter (or theobroma oil) without the cocoa solids.

Although many different types of cocoa beans grow throughout the world, three varieties of cocoa beans are mainly used to make chocolate products: (a) criollo (meaning 'native'), distributed to the north and west of the Andes, (b) forastero (meaning 'foreign'), found mainly in the Amazon basin, and (c) trinitario (meaning 'sent from heaven') (Bruinsma & Taren 1999).

Cocoa beans from different countries along with postharvesting and processing procedures can have a striking influence on the flavanol content of chocolate and cocoa (Hollenberg et al 2004). As flavanols impart a bitter, astringent flavour, chocolate often undergoes extensive processing, dilution and the addition of flavour modifiers to improve its palatability despite these processes having the potential to negatively impact on cocoa's nutritional and clinical value (McShea et al 2008). While a study that examined the total phenolic content of chocolate found that the antioxidant properties of the artisan-made chocolate were significantly better than those of the factory-produced chocolate (Cervellati et al 2008), recent attention to flavonoid content has led to the development of commercial processes that protect and preserve the naturally occurring flavonoids with Cocoapro™ being developed by Mars Inc and Acticoa™ by the Swiss-based Barry Callebaut.

CHEMICAL COMPONENTS

Cocoa is among the most concentrated sources of the flavanols, catechin and epicatechin, with four times the catechin content of tea (Arts et al 1999). Chocolate also contains additional flavonoids not found in tea, with high concentrations of oligomeric procyanidins (Lazarus et al 1999). Dark chocolate has the highest total catechin content with approximately 53.5 mg/100 g, whereas milk chocolate contains approximately 15.9 mg/100 g (Arts et al 1999). White chocolate primarily contains cocoa butter with minimal levels of polyphenols.

In addition to flavanols, cocoa also contains the methylxanthines, caffeine and theobromine, the biogenic amines phenylethylamine, phenylalanine and tyrosine (Bruinsma & Taren 1999) and the cannabinoid-like fatty acid anandanine analogues, *N*-oleoylethanolamine and *N*-linoleoylethanolamine (Di Tomaso et al 1996). Chocolate is also a rich source of minerals, including magnesium, calcium, iron, copper, phosphorus, potassium and zinc (Steinberg et al 2003) and it is suggested that the presence of methylxanthines, peptides and minerals could synergistically enhance or reduce cocoa's antioxidant properties (Jalil & Ismail 2008).

MAIN ACTIONS

Both in vitro and in vivo studies indicate that cocoa flavanols have antioxidant effects, decrease LDL cholesterol oxidation, reduce platelet aggregation and enhance endothelial function. There is, however, tremendous variability in cocoa processing, flavonoid content and measurement of flavonoids,

and questions remain around bioavailability and dosing frequency (Fisher & Hollenberg 2006). A feeding study demonstrated that procyanidins were remarkably stable in the stomach environment and thus most ingested procyanidins reach the small intestine intact and are available for absorption or metabolism (Rios et al 2002). Epicatechin and its metabolites reach maximal levels 2 hours after either chocolate or cocoa intake, with rapid excretion in the urine (Baba et al 2000) and dimeric procyanidins have been detected in human plasma as early as 30–60 min after the consumption of flavanol-rich beverages providing 0.25–0.50 g/kg cocoa/kg body weight (Holt et al 2002, Zhu et al 2005).

Cocoa powder dissolved in milk as one of the most common ways of cocoa powder consumption seems to have a negative effect on the absorption of polyphenols; however, statistical analyses have shown that milk does not impair the bioavailability of flavonoids (Keogh et al 2007, Roura et al 2007). High-flavonoid cocoa products may lead to greatly enhanced flavonoid bioavailability in humans (Tomas-Barberan et al 2007).

Antioxidant

Cocoa has been found to have much higher levels of total phenolics and flavonoids, with a corresponding higher antioxidant capacity per serving, than black tea, green tea or red wine (Lee et al 2003). It has been suggested that the antioxidant capacity of cocoa polyphenols is greater than synthetic antioxidants and that they have the potential to complement or replace synthetic antioxidants in aqueous and oil-based food applications (Osman et al 2004).

Human studies have confirmed that the polyphenols in chocolate are indeed bioavailable and able to increase the antioxidant capacity of plasma, with one study reporting that ingestion of 80 g of procyanidin-rich chocolate increased plasma epicatechin concentrations 12-fold, significantly increased plasma total antioxidant capacity by 31% and significantly decreased 2-thiobarbituric acid reactive substances by 40% after 2 hours, with levels returning to normal within 6 hours (Rein et al 2000a).

Cocoa has been consistently shown to confer significant protection against oxidation both in vitro (Martin et al 2008, Sies et al 2005, Waterhouse et al 1996) and in vivo (Kondo et al 1996). In addition to reducing lipid oxidation, consumption of a flavanol-rich cocoa beverage has been shown to reduce susceptibility of erythrocytes to haemolysis and to increase their ability to buffer free radicals (Zhu et al 2005).

There is evidence that the polyphenols are not the only antioxidants in chocolate, as suggested by a study that found that consumption of chocolate containing 200 mg of polyphenols, as well as chocolate with less than 10 mg of polyphenols, reduced faecal free radical production (Record et al 2003). Furthermore, similar reductions in markers of lipid peroxidation have been observed after daily consumption of 75 g of dark chocolate and dark chocolate enriched with cocoa polyphenols, as well as with white chocolate, which contains very little polyphenols (Mursu et al 2004).

In a crossover study in 23 healthy subjects, cocoa powder and dark chocolate was seen to modestly reduce LDL oxidation susceptibility while increasing serum total antioxidant capacity and HDL cholesterol concentrations (Wan et al 2001), and another crossover trial of 25 healthy subjects found that supplementation with 36.9 g of dark chocolate (30 g of cocoa powder drink) for 6 weeks reduced LDL oxidisability (Mathur et al 2002). Similar results were seen in a randomised, double-blind crossover trial that found that a high-flavanol cocoa drink providing 187 mg flavan-3-ols/100 mL significantly reduced lipid peroxidation, compared with a low-flavanol cocoa drink providing only 14 mg/100 mL (Wiswedel et al 2004).

In contrast to these studies a further randomised, double-blind, placebo-controlled study of 21 healthy adults, however, found that intake of high-flavonoid (213 mg procyanidins, 46 mg epicatechin) dark chocolate bars for 2 weeks did not alter resistance to LDL oxidation, total antioxidant capacity, 8-isoprostanes, blood pressure, lipid parameters, body weight or BMI, despite increasing plasma epicatechin concentrations and improving endothelium-dependent flow-mediated dilation of the brachial artery (Engler et al 2004).

Effects on microcirculation and nitric oxide

Flavanols have been shown in several in vitro or ex vivo studies to modify the production of proinflammatory cytokines, the synthesis of eicosanoids, the activation of platelets and nitric oxide-mediated mechanisms (Selmi et al 2008). A double-blind, dose-finding study found that flavanol-rich cocoa increased circulating NO species in the plasma of male smokers, with maximal effects seen with ingestion of 176–185 mg flavanols (Heiss et al 2005). Another double-blind trial found that ingestion of a high-flavanol cocoa drink, but not a low-flavanol one, enhanced NO bioactivity and increased plasma concentrations of nitroso compounds and flow-mediated dilation of the brachial artery (Sies et al 2005). Similarly, ingestion of flavanol-rich cocoa is associated with acute elevations in levels of circulating NO species, enhanced flow-mediated dilatation response of conduit arteries, and an augmented microcirculation, with these effects being mimicked by ingestion of chemically pure epicatechin. Moreover, chronic consumption of a cocoa–flavanol-rich diet has been associated with augmented urinary excretion of NO metabolites (Schroeter et al 2006).

Double-blind, crossover intervention studies in both humans and rats suggest that an increase in the circulating NO pool following flavanol consumption is correlated with decreased arginase activity as the availability of L-arginine can be a rate-limiting factor for cellular NO production by nitric oxide synthase (NOS) (Schnorr et al 2008).

Lipid-lowering

A 3-week clinical supplementation trial of 45 non-smoking, healthy volunteers consuming high-polyphenol chocolate found a significant increase

in serum HDL cholesterol with dark and high-polyphenol chocolate (11.4% and 13.7%, respectively), whereas white chocolate consumption resulted in a small decrease in HDL. Markers of lipid peroxidation decreased 11.9% in all three study groups with no changes occurring in the total antioxidant capacity of plasma, in the oxidation susceptibility of serum lipids or VLDL and LDL, or in the concentration of plasma F2-isoprostanes or hydroxy fatty acids. This suggests that while cocoa polyphenols may increase the concentration of HDL cholesterol, chocolate fatty acids may modify the fatty acid composition of LDL, making it more resistant to oxidative damage (Mursu et al 2004).

A new soluble cocoa fibre product rich in soluble dietary fibre and antioxidant polyphenols diminished the negative impact of the cholesterol-rich diet in an animal model of dietary-induced hypercholesterolaemia (Ramos et al 2008). Similarly, in an animal model of hypercholesterolaemia a cholesterol- and triglyceride-lowering effect along with a reduction of biomarkers of oxidative stress and increasing faecal bulking was seen after 3 weeks of consuming a fibre-rich cocoa product (Bravo et al 2008).

Inhibits platelet function

Numerous dietary intervention studies in humans and animals indicate that flavanol-rich foods and beverages might exert cardioprotective effects with respect to vascular function and platelet reactivity (Keen et al 2005). Acute doses of flavanols and oligomeric procyanidins from cocoa have been observed to inhibit platelet activation (Pearson et al 2002, Rein et al 2000b) and have an aspirin-like effect on primary haemostasis 2 and 6 hours after consumption (Hermann et al 2006, Pearson et al 2002, Rein et al 2000b), with the effects being similar to, but less profound than, aspirin (Pearson et al 2002). Similar results have been observed in longer studies with lower doses of cocoa flavanols, with a double-blind, controlled trial demonstrating significantly lower platelet aggregation and significantly higher plasma ascorbic acid concentrations after supplementation with cocoa flavanols (234 mg cocoa flavanols and procyanidins/day) over 28 days (Murphy et al 2003).

In another randomised trial of 30 healthy volunteers, 100 mg of dark chocolate, but not white or milk chocolate, were found to significantly inhibit collagen-induced platelet aggregation (Innes et al 2003). The alteration of eicosanoid synthesis has been suggested as a plausible mechanism by which procyanidins can decrease platelet activation, and this has been observed in an in vitro study of the effect of procyanidin on aortic endothelial cells, as well as in a randomised, blinded, crossover study of high procyanidin chocolate (4.0 mg/g) (Schramm et al 2001).

Antidiabetic

Pretreatment with a cocoa extract high in polyphenols was seen to normalise body weight, plasma glucose levels, total cholesterol, triglycerides and high-density lipoprotein levels in streptozotocin-diabetic rats (Ruzaidi et al 2008). In humans, short-term administration of flavonoid-rich dark chocolate significantly improved insulin sensitivity and endothelial function in healthy and hypertensive subjects (Grassi et al 2008b), while a double-blind, placebo-controlled crossover study found that flavanol-rich dark chocolate but not flavanol-free white chocolate ameliorated insulin sensitivity and beta-cell function, decreased blood pressure and increased flow-mediated dilation in hypertensive patients with impaired glucose tolerance (Grassi et al 2008a). Similar results were obtained from another small, randomised controlled trial that found that high-flavanol cocoa reversed vascular dysfunction in diabetic patients (Balzer et al 2008). In contrast to these findings, a double-blind, crossover study found that daily consumption of flavanol-rich cocoa for 2 weeks was not sufficient to reduce blood pressure or improve insulin resistance in human subjects with essential hypertension (Muniyappa et al 2008).

Psychological effects

Chocolate is purported to have a range of psychological effects, including enhanced arousal and cognitive function, stimulation of feelings of wellbeing and euphoria, as well as initiating cravings. The orosensory aspects of chocolate, including its taste, smell and texture, certainly contribute to chocolate's positive appeal. Chocolate contains large amounts of fat in the form of cocoa butter, which melts at body temperature producing a pleasurable melt-in-the-mouth experience. Chocolate also often contains large amounts of sugar and thus satisfies the seemingly innate preference for sweet, high-fat, foods (Bruinsma & Taren 1999).

In addition to unique sensory properties, chocolate also contains many pharmacologically active substances. Several endogenous biogenic amines with sympathomimetic properties are found in chocolate, most notably tyramine and phenylethylamine (Hurst 1982). Phenylethylamine is an amphetamine analogue structurally related to methylenedioxy–methamphetamine that may act to potentiate dopaminergic and noradrenergic neurotransmission and modulate mood (Bruinsma & Taren 1999).

Cocoa is also known to contain methylxanthines, including caffeine and theobromine, both of which are stimulants. Although the stimulatory and sympathomimetic effects of caffeine are well documented, the psychological effects of theobromine are less certain.

A group of biologically active constituents, including *N*-oleoylethanolamine and *N*-linoleoylethanolamine, have been identified in chocolate and appear to be related to anandamide, the 'internal bliss' chemical, which is the endogenous lipoprotein that binds cannabinoid receptors within the brain (Di Tomaso 1996). Although it has been suggested that these compounds may elicit heightened sensitivity and euphoria by directly activating cannabinoid receptors or by increasing anandamide levels (Bruinsma & Taren 1999), measurements have suggested that their amounts in cocoa is several orders of magnitude below those required to

reach the blood and cause observable central effects (Di Marzo et al 1998).

Chocolate craving, which is reported to be the most common food craving (Weingarten & Elston 1991), is more common in women, with fluctuations occurring with hormonal changes just before and during the menses (Rozin et al 1991). The basis for chocolate craving, however, remains undetermined, but it is suggested that aroma, sweetness, texture and calorie content are likely to play a more important role in chocolate cravings than pharmacological factors (Bruinsma & Taren 1999, Michener & Rozin 1994, Rozin et al 1991, Smit et al 2004).

Modulation of immune function and inflammation

The procyanidin fraction from cocoa demonstrates immunomodulatory function in vitro, with stimulation of TNF-alpha (Mao et al 2002) and modulation of the secretion of the cytokine transforming growth factor (TGF-beta-1) (Mao et al 2003), as well as inhibiting induced nuclear transcription of human IL-1B (Mao et al 2000a), phytohaemagglutinin-induced stimulation of IL-2 (Mao et al 1999) and mitogen-stimulated secretion of IL-4 (Mao et al 2000b) in peripheral blood mononuclear cells in vitro. In vivo cocoa intake has been shown to modulate intestinal immune responses in young rats (Ramiro-Puig et al 2008), while cocoa polyphenols have been shown to reduce leukotriene synthesis through inhibition of human 5-lipoxygenase in humans (Sies et al 2005).

Anti-inflammatory

While flavanols are known to modify the production of proinflammatory cytokines, the synthesis of eicosanoids, the activation of platelets, and nitric oxide-mediated mechanisms (Selmi et al 2008), evidence for any beneficial effects of cocoa flavanols in providing a meaningful anti-inflammatory action has been gathered predominantly from in vitro experiments. Additional research in well-designed human clinical experiments is therefore required to determine if flavanol-rich cocoa could be used to treat or prevent chronic diseases linked to dysfunctional inflammatory responses (Selmi et al 2006).

Altered cellular signalling

Flavonoids have been shown to modulate tumour pathology in vitro and in animal models, and the pentameric procyanidin fraction isolated from cocoa is reported to slow the growth of cultured human aortic endothelial cells (Kenny et al 2004a), as well as inhibit the proliferation of human dermal microvascular endothelial cells in vitro through inhibition of tyrosine kinase ErbB2 expression. This has led to the suggestion that polyphenols may influence endothelial growth signalling in vitro, with potential beneficial effects for specific neoplasias in which cells over-express ErbB2 (Kenny et al 2004b).

Inhibition of dental caries

Cocoa contains substances that protect against dental caries (Palenik et al 1977, s'Gravenmade et al 1977) and in vitro experiments have shown that monomeric polyphenols and tannins from cocoa may interfere with glucosyltransferase activity of *Streptococcus mutans* and reduce plaque formation (Kashket et al 1985). Similar results were reported in hamsters, with a marked caries-inhibitive effect found with a water extract of cocoa (Stralfors 1966). Cocoa bean husk, while not used in cocoa or chocolate, demonstrates antibacterial properties attributed to its unsaturated fatty acids and antiglucosyltransferase activities attributed to epicatechin polymers, as well as being shown both in vitro and in vivo to possess significant antiplaque activity (Matsumoto et al 2004).

Antitussive

It has been suggested that theobromine, a methylxanthine derivative present in cocoa, may form the basis for a new class of antitussive drugs, as it has been shown to effectively inhibit citric acid-induced cough in guinea pigs in vivo, as well as suppress capsaicin-induced cough in a human double-blind trial. The observation that theobromine inhibits capsaicin-induced sensory nerve depolarisation of the guinea pig and human vagus nerve suggests that its antitussive action may be mediated peripherally through an inhibitory effect on afferent nerve activation (Usmani et al 2005).

Skin anti-ageing and photoprotecion

Long-term cocoa ingestion appears to lead to an increased resistance against UV-induced erythema and a lowered transepidermal water loss. In a crossover design study in 10 healthy women, a single dose of cocoa rich in flavanols (329 mg) was found to enhance dermal blood flow by 1.7-fold and elevate oxygen saturation of haemoglobin at 1 mm skin depth 1.8-fold 2 hours after consumption, while there was no effect seen after consumption of low-flavanol cocoa (27 mg) (Neukam et al 2007).

In a study using a model of ex vivo human skin explants, cocoa polyphenols were seen to exhibit a positive action on several indicators of skin elasticity and skin tonus, and an enhancing effect of cocoa butter on activity of cocoa polyphenol was observed (Gasser et al 2008).

There is evidence to suggest that dietary flavanols from cocoa contribute to endogenous photoprotection, improve dermal blood circulation, and affect cosmetically relevant skin surface and hydration variables in women. A 12-week randomised controlled trial, comparing high flavanol (326 mg/day containing epicatechin (61 mg/day) and catechin (20 mg/day) and low flavanol (27 mg/day containing 6.6 mg epicatechin and 1.6 mg catechin) cocoa consumption, found high flavanol consumption led to significantly reduced UV-induced erythema (by 15% and 25%, after 6 and 12 weeks of treatment). The high flavanol group also experienced increased skin density, skin hydration and skin thickness along with increased blood flow in cutaneous and subcutaneous tissues, and significantly decreased skin roughness and scaling compared with no change in the low-flavanol group (Heinrich et al 2006).

Antineurodegenerative

The major flavonoids of cocoa, epicatechin and catechin, protected cellular membrane from amyloid beta-protein-induced neurotoxicity in vitro, suggesting that cocoa may have antineurodegenerative effects (Heo & Lee 2005). This is supported by a study that found that 1-year administration of a cocoa polyphenolic extract (Acticoa powder), affects the onset of age-related cognitive deficits, urinary free dopamine levels and lifespan in old Wistar-Unilever rats (Bisson et al 2008a, 2008b). Daily oral administration of Acticoa powder was also seen to protect rats from cognitive impairments after heat exposure by counteracting the overproduction of free radicals (Rozan et al 2007).

OTHER ACTIONS

Acticoa powder has been observed to protect rats from prostate carcinogenesis (Bisson et al 2008a) and prostate hyperplasia as well as improve established prostate hyperplasia in an animal model (Bisson et al 2007). The clinical significance of these findings is yet to be determined.

CLINICAL USE

Cardiovascular disease

There is evidence to support that the flavanols in cocoa can be absorbed, are bioactive, and may be responsible for the cardiovascular benefits associated with regular cocoa consumption. Several mechanisms have been proposed to explain this positive influence, including metabolic, antihypertensive, anti-inflammatory and antioxidant effects along with decreased platelet activation and function, effects on serum lipids, insulin sensitivity, immune function and vascular endothelial function (Ding et al 2006, Eo 2008, Lippi et al 2008).

While there are no randomised controlled trials that studied effects on cardiovascular morbidity or mortality (Hooper et al 2008), there is accumulating evidence over the past decade demonstrating that moderate consumption of chocolate, especially dark chocolate, may exert protective effects against the development of cardiovascular disease. Epidemiologic studies have shown inverse associations between dietary polyphenols and mortality from coronary heart disease. Small, short-term, intervention studies have indicated that cocoa-containing foods may provide many cardiovascular benefits, including reducing blood pressure, inhibiting platelet function, preventing lipid oxidation, reducing LDL, increasing HDL, improving endothelial function, increasing insulin sensitivity, reducing insulin resistance and reducing inflammation.

A meta-analysis of 133 trials on flavonoid-rich foods and cardiovascular risk found that chocolate increased flow-mediated dilatation after acute (3.99%; 95% CI: 2.86, 5.12; 6 studies) and chronic (1.45%; 0.62, 2.28; 2 studies) intake and reduced systolic (−5.88 mmHg; −9.55, −2.21; 5 studies) and diastolic (−3.30 mmHg; −5.77, −0.83; 4 studies) blood pressure (Hooper et al 2008, Innes et al 2003). A 2006 systematic review of 136 experimental, observational and clinical studies on cocoa products and the risk of cardiovascular disease concluded that stearic acid may be neutral, while flavonoids are likely protective against cardiovascular mortality. The review found that multiple short-term, randomised feeding trials suggest cocoa and chocolate may exert beneficial effects on cardiovascular risk with a meta-analysis finding that flavonoids may lower risk of cardiovascular mortality, RR = 0.81 (95% CI: 0.71–0.92) comparing highest and lowest tertiles (Ding et al 2006).

While there are no published long-term, randomised controlled trials or prospective intervention studies of cocoa with hard clinical end points (Hooper et al 2008, Maron 2004), the cardiovascular benefits of cocoa are evident in a 15-year epidemiological study of 470 elderly men, which found that cocoa intake was inversely associated with blood pressure and 15-year cardiovascular and all-cause mortality. This study found a 50% reduction in cardiovascular-related death and all-cause mortality in men with the highest tertile of cocoa intake compared to the lowest tertile, suggesting that the pharmacological actions described for cocoa do, in fact, translate into reduced cardiovascular risk and other positive clinical outcomes (Buijsse et al 2006).

Hyperlipidaemia

While the lipid content of chocolate is relatively high, around one-third of the lipid in cocoa butter is composed of the fat, stearic acid, which exerts a neutral cholesterolaemic response in humans by an unknown mechanism (Kris-Etherton et al 1993, Steinberg et al 2003). Cocoa butter, however, is considered a high calorie fat because it has a high digestibility with a digestible energy value of 37 kJ/g in humans (Shahkhalili et al 2000). The results of a randomised, double-blind, cross-over design supplementation study suggest that the addition of calcium to chocolate can significantly reduce the absorption of cocoa butter, thus reducing the absorbable energy value of the chocolate by approximately 9% while at the same time reducing the plasma LDL cholesterol level and leaving the plasma HDL cholesterol level and taste of the chocolate unchanged (Shahkhalili et al 2001).

A double-blind study of 160 subjects that examined the effects of 13, 19.5 and 26 g/d of cocoa powder over 12 weeks found improved plasma lipid profiles in all groups with decreased plasma LDL, oxidised LDL and apo B and increased HDL concentrations in normocholesterolaemic and mildly hypercholesterolaemic human subjects (Baba et al 2007a, 2007b). Other short-term studies have demonstrated that cocoa flavanols can reduce serum LDL (Fraga et al 2005, Grassi et al 2005b) and increase HDL (Mursu et al 2004, Wan et al 2001) but long-term clinical trials are needed to determine its role in the clinical treatment of hypercholesterolaemia.

Cocoa bran may also have a use in hypercholesterolaemia, as well as constipation, because this low-fat, high-fibre material has been shown in a randomised, controlled, double-blind study to increase faecal bulk similarly to wheat bran and reduce the LDL/HDL cholesterol ratio, with

no effect on LDL cholesterol oxidation (Jenkins et al 2000).

Blood pressure

A meta-analysis of five randomised controlled studies involving a total of 173 subjects with a median duration of 2 weeks found significant reductions in both systolic and diastolic blood pressure in those consuming cocoa compared with cocoa-free controls (Taubert et al 2007). Clinical studies on flavanol-containing dark chocolate have demonstrated significant reductions in blood pressure in various populations, including normotensive people with mild hypercholesterolaemia (Erdman et al 2008), overweight adults (Davison et al 2008, Faridi et al 2008), patients with newly diagnosed essential hypertension (Grassi et al 2005b), patients with untreated upper-range prehypertension and stage 1 hypertension without concomitant risk factors (Taubert et al 2007) and healthy people (Grassi et al 2005a, Vlachopoulos et al 2007), including male soccer players (Fraga et al 2005).

While cocoa appears to have mild antihypertensive actions this is complemented by positive effects on other cardiovascular risk factors such as serum lipids, blood glucose and vascular function. These benefits are evident from the results of various clinical trials. For example, a randomised controlled trial using 100 g of dark chocolate containing approximately 500 mg of polyphenol consumed daily for 15 days found reductions in diastolic blood pressure by -11.9 ± 7.7 mmHg, decreases in serum LDL cholesterol from 3.4 to 3.0 mmol/L, improvements in flow-mediated dilation, and reductions in insulin resistance and increase insulin sensitivity in patients with newly diagnosed essential hypertension (Grassi et al 2005b). More recently, an 8-week double-blind, placebo-controlled, crossover study found that consumption of a cocoa flavanol-containing dark chocolate bar with added plant sterols lowered serum lipids and blood pressure in normotensive population with elevated cholesterol (Allen et al 2008). Yet another study found that 12 weeks of supplementation with high-flavanol cocoa led to reduced insulin resistance, diastolic BP and mean arterial BP and improved endothelial function independent of exercise in overweight and obese subjects (Davison et al 2008).

Vascular function

In a recent meta-analysis it was found that chocolate increases flow-mediated dilatation after acute and chronic intake (Hooper et al 2008).

A review of evidence from both animal and human studies suggests that human ingestion of the flavanol epicatechin is, at least in part, causally linked to the reported beneficial effects on vascular effects (Schroeter et al 2006) while results from a controlled trial suggest that formation of vasodilative nitric oxide contribute to beneficial vascular effects (Taubert et al 2007). A randomised, placebo-controlled, single-blind, crossover trial of 45 healthy adults further suggests that endothelial function improves significantly more with sugar-free than with regular cocoa and that sugar content may attenuate positive vascular effects while sugar-free preparations may augment them (Faridi et al 2008).

Improved vascular function after cocoa consumption has been demonstrated in a number of recent clinical trials involving hypercholesterolaemic postmenopausal women (Wang-Polagruto et al 2006), heart transplant recipients (Flammer et al 2007), and healthy subjects (Faridi et al 2008, Vlachopoulos et al 2007). It has also been found that flavanol-rich cocoa enhanced several measures of endothelial function to a greater degree among older than younger healthy subjects leading to the suggestion that the vascular effects of flavanol-rich cocoa may be greater among older people in whom endothelial function is more disturbed (Fisher & Hollenberg 2006).

There is evidence to suggest that the improved vascular function with flavanol-rich cocoa occurs acutely and in a sustained and dose-dependent manner with a maximal flow-mediated dilatation at 2 hours after a single-dose ingestion of flavanol-rich cocoa seen in a trial involving individuals with smoking-related endothelial dysfunction (Heiss et al 2007). Similar acute results were seen in a double-blind, randomised controlled trial involving 22 heart transplant recipients in which flavonoid-rich dark chocolate was seen to induce coronary vasodilation, improve coronary vascular function, decrease platelet adhesion and reduce serum oxidative stress 2 hours after consumption compared to cocoa-free control chocolate (Flammer et al 2007). Further evidence for acute effects comes from a study in which dark chocolate, but not white chocolate, was observed to significantly improve endothelial and platelet function in healthy smokers, with increased flow-mediated dilatation, increased total antioxidant status and reduced shear stress-dependent platelet function seen 2–8 hours after ingestion (Hermann et al 2006).

The above findings are contrasted by a 6-week double-blind, placebo-controlled, fixed-dose, parallel-group clinical trial of 101 healthy older adults that compared consumption of a 37 g dark chocolate bar or 237 mL of artificially sweetened cocoa beverage with placebo. This study failed to demonstrate the predicted beneficial effects of short-term dark chocolate and cocoa consumption on neuropsychological or cardiovascular health-related variables (Crews et al 2008).

Cardiac ischaemia

There is evidence suggesting that cocoa flavanols may help in reducing cardiac ischaemia with an animal study finding that epicatechin pretreatment confers cardioprotection in the setting of ischaemia reperfusion injury and that the effects are independent of changes in haemodynamics, sustained over time, and accompanied by reduced levels of indicators of tissue injury (Yamazaki et al 2008). Human studies suggest that cocoa consumption may have clinical benefits for cerebrovascular ischaemic syndromes, including dementias and stroke with dietary intake of flavanol-rich cocoa being associated with a significant increase in cerebral blood flow velocity in 34 healthy elderly humans (Sorond et al 2008). It

is further suggested that the prospect of increasing cerebral perfusion with cocoa flavanols is extremely promising with implications for stroke and dementia (Fisher et al 2006).

Premenstrual syndrome

Magnesium deficiency may contribute to PMS symptoms, which may be improved by chocolate or cocoa powder, which contain a high concentration of magnesium (≈ 100 mg/100 g in chocolate and 520 mg/100 g in cocoa powder). There is also some evidence to suggest that serotonin levels are low premenstrually, and it is possible that premenstrual chocolate cravings are the body's attempt to raise CNS concentrations of serotonin (Bruinsma & Taren 1999).

Enhanced cognitive function

The results of a double-blind, placebo-controlled study suggests that both milk and dark chocolate, but not white chocolate, improve cognitive function. A second double-blind study suggests that this improvement is due to the methylxanthin content of chocolate, with 11.6 g of cocoa powder producing identical improvements in cognitive function and the mood construct 'energetic arousal' as a mixture of caffeine (19 mg) and theobromine (250 mg) (Smit et al 2004).

Consumption of a 65 g chocolate bar was shown to significantly increase driving accuracy and reduce collisions compared to an equicaloric snack of cheese and biscuits or no snack in a controlled trial of 12 volunteers (Smith & Rich 1998).

Food source

Cocoa and chocolate are nutritious foods that contribute to caloric as well as trace mineral intake (Steinberg et al 2003). Milk chocolate has a relatively low glycaemic index of approximately 40 (Foster-Powell et al 2002) and this is attributed to the fat in chocolate slowing gastric emptying and thus the rate of subsequent digestion and absorption. The glycaemic effect of milk chocolate can be further reduced by replacing the sucrose with fructose or isomalt (Gee et al 1991). Foods containing cocoa have been shown to lead to a greater postprandial insulin secretion in healthy young adults than foods with alternative flavourings, despite having a similar glycaemic index. It is suggested that specific insulinogenic amino acids or greater cephalic phase insulin release may explain this finding, although the clinical implications are uncertain (Miller et al 1995).

Milk chocolate has also been shown to be a cheap, effective and palatable form of fatty meal for producing gall bladder contraction prior to cholecystography (Harvey 1977).

Colonic health and constipation

Cocoa mass has been suggested to have beneficial effects on metabolism of colonic microbiota (Mäkivuokko et al 2007) and cocoa husk rich in dietary fibre may assist paediatric patients with idiopathic chronic constipation. This is supported by an RCT that found that benefits seem to be more evident in paediatric constipated patients with slow colonic transit time (Castillejo et al 2006).

OTHER USES

Chocolate consumption 15 min before exercise has been shown to enhance exercise capacity, spare glycogen stores, delay fatigue and contribute to the recovery of glycogen repletion in healthy subjects (Chen et al 1996).

Cocoa may also be of use in lactose intolerance, with a feeding study of 35 subjects finding that the addition of cocoa significantly reduced breath hydrogen levels, as well as bloating and cramping, with the result being independent of the presence of sucrose and carrageenan (Lee & Hardy 1989).

Cocoa butter is used in the formation of suppositories and pessaries, as well as preparations for rough or chafed skin, chapped lips, sore nipples and various cosmetics (Raintree Nutrition 1996).

There is empiric evidence indicating successful treatment of copper deficiency by adding copper-rich cocoa powder to tube feeding formulas. It is suggested that although there are other high copper containing foods such as seaweed, oyster and beans, cocoa powder is advantageous due to the ease of adding it to feeding formulas (Tokuda et al 2006, Tokuda 2007).

DOSAGE RANGE

There is enormous variability in the polyphenol content of cocoa and chocolate and the flavanols in cocoa exist in a multitude of different stereochemical configurations, thus giving rise to a unique and complex mixture of compounds. Given this complexity, the quantitative analysis of cocoa flavanols can be challenging. It is only through the use of methods that can accurately quantify these flavanols that it will be possible to make meaningful dietary recommendations regarding the consumption of cocoa flavanol-containing foods (Kwik-Uribe & Bektash 2008).

Trials suggest that effective doses are approximately 40–100 g dark chocolate or 15–30 g cocoa powder, providing approximately 200–500 mg polyphenols.

TOXICITY

Cocoa contains caffeine, which is a mild CNS stimulant that can be profoundly toxic in large doses, resulting in arrhythmia, tachycardia, vomiting, convulsions, coma and death. The caffeine content of cocoa is variable, being approximately 0.009% by weight (Kondo et al 1996), with a typical milk chocolate bar containing approximately 10 mg of caffeine, compared to a cup of coffee, which contains approximately 100 mg (Bruinsma & Taren 1999). Fatal caffeine overdoses in adults have been reported, but are rare and typically require ingestion of more than 5 g of caffeine which would require consumption of more than 50 kg of chocolate (Kerrigan & Lindsey 2005).

ADVERSE REACTIONS

It is believed that chocolate is a trigger for migraine, yet there is inconsistent support for this. In one

small double-blind, parallel-group study of 12 patients who believed that chocolate could provoke their attacks, chocolate ingestion was more likely than placebo to trigger a typical migraine episode, with the median time until the onset of the attack of 22 h (Gibb et al 1991). Three other double-blind, placebo-controlled trials suggest that chocolate on its own rarely precipitates migraine (Marcus et al 1997, Moffett et al 1974), with the results of one trial suggesting that chocolate was no more likely to provoke headache than was carob in typical migraine, tension-type or combined headache sufferers (Marcus et al 1997).

Allergy to cocoa has been documented (Taibjee et al 2004) and it has been suggested that workers employed in the processing of cocoa and flour may be at a high risk for the development of allergic sensitisation and respiratory impairment (Zuskin et al 1998). One case report of cocoa aspiration causing severe aspiration pneumonitis in a 4-year-old has been documented (Lopatka et al 2004).

There is no evidence that chocolate contributes to acne (Ravenscroft 2005).

SIGNIFICANT INTERACTIONS

Polyphenols may reduce iron absorption, with a cocoa beverage containing 100–400 mg total polyphenols per serving having been shown to reduce iron absorption by approximately 70% (Hurrell et al 1999).

PREGNANCY USE

Cocoa and chocolate can be considered safe to use in pregnancy.

PRACTICE POINTS/PATIENT COUNSELLING

- Cocoa has many potential benefits for the cardiovascular system and may reduce blood pressure, inhibit platelet function, and improve the serum cholesterol profile, as well as having beneficial effects on insulin sensitivity. However, further research is required to confirm the benefits.
- Cocoa may act to enhance cognitive function in a similar way to coffee albeit with one-tenth the caffeine content.
- The most active agents in cocoa are the polyphenols, which are present in high amounts in dark chocolate, with lesser amounts in milk chocolate and minimal amounts in white chocolate.
- Cocoa powder contains minimal fat while dark chocolate contains less fat and sugar than milk or white chocolate. Beneficial effects are more likely to result from the use of cocoa powder or dark chocolate containing more than 50–60% cocoa mass.

PATIENTS' FAQs

What will this herb do for me?

Cocoa is a nutritious food that appears to have beneficial effects on blood pressure, cholesterol, blood clotting and psychological wellbeing.

When will it start to work?

Psychological effects of chocolate consumption may be evident immediately, whereas beneficial effects on blood pressure and cholesterol may be evident after 2–4 weeks.

Are there any safety issues?

Cocoa powder and dark chocolate are extremely safe and are unlikely to precipitate migraine, acne or dental caries or produce adverse effects from the caffeine content.

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Coenzyme Q10

OTHER NAMES

Ubiquinone, ubidecarenone, ubiquinol

BACKGROUND AND RELEVANT PHARMACOKINETICS

Coenzyme Q10 (CoQ10) is an endogenous enzyme cofactor produced in humans from tyrosine through a cascade of reactions that itself requires eight vitamin coenzymes: tetrahydrobiopterin, vitamins B6, C, B2, B12, folic acid, niacin, and pantothenic acid (Folkers et al 1990). CoQ10 is also a fat-soluble antioxidant vitamin that plays an indispensable role in intracellular energy production.

Absorption occurs in the small intestine and tends to be poor, and is influenced by the presence of food and drink. CoQ10 is better absorbed in the presence of a fatty meal and is primarily bound to VLDL and LDL cholesterol. As such, serum levels of CoQ10 depend mostly on the amount of CoQ10-containing lipoproteins in circulation.

After incorporation into lipoproteins in the liver, CoQ10 is subsequently concentrated in various tissues, including the adrenals, spleen, kidneys, lungs and myocardium. Physical activity markedly reduces muscle tissue levels of CoQ10, which do not correlate to serum levels, suggesting that they are independently regulated (Laaksonen et al 1995a, Overvad et al 1999).

CHEMICAL COMPONENTS

The basic structure of ubiquinones is a benzoquinone head and terpinoid tail. The number of isoprenoid units in the tail portion varies among coenzymes. CoQ10 contains one quinine group and 10 isoprenyl units (Overvad et al 1999). Ubiquinones have been found in microorganisms, plants and animals but the CoQ10 form is the most common type found in mammals and humans.

FOOD SOURCES

Meat and fish products are the most concentrated sources of CoQ10, although lesser quantities are found in boiled broccoli, cauliflower, nuts, spinach and soy.

DEFICIENCY SIGNS AND SYMPTOMS

No recommended daily intake (RDI) levels have been established but there has been some speculation as to possible deficiency signs and symptoms. These include fatigue, muscle aches and pains and chronic gum disease.

Based on biopsy and/or serum samples, it has been observed that relative CoQ10 deficiency is associated with:

- congestive heart failure (Sole & Jeejeebhoy 2002, Spigset 1994a, Molyneux et al 2008)
- cardiomyopathy (Mortensen et al 1990)
- hypertension (Karlsson et al 1991)
- ischaemic heart disease (Karlsson et al 1991)
- hyperthyroidism (Bianchi et al 1999)
- breast cancer (Folkers et al 1997)
- cystic fibrosis (Laguna et al 2008)
- pancreatic insufficiency (Laguna et al 2008).

At this stage, it is still unclear whether an observation of relative deficiency in a particular disease state can be interpreted as part of the aetiology of that disease or whether lowered levels are a consequence of disease. In heart failure the situation is somewhat clearer, as patients with more advanced heart failure have significantly lower CoQ10 levels than those with less advanced conditions (Mortensen 1993).

A deficiency state may result from:

- impaired or reduced synthesis due to nutritional deficiencies, advancing age or medication use.
- interactions with drugs — there is clinical evidence that lovastatin, pravastatin and simvastatin reduce CoQ10 status in humans, which may, in part, explain the incidence of side effects, particularly myopathy, associated with their use (Bargossi et al 1994a, 1994b, Folkers et al 1990, Mortensen et al 1997). Clinical evidence also suggests that use of gemfibrozil and other fibric acid derivatives reduce CoQ10 levels (Aberg et al 1998). In vitro evidence suggests that other drugs, such as clonidine, hydralazine, hydrochlorothiazide, methyldopa, metoprolol and propranolol, may also decrease endogenous production of CoQ10 (Kishi et al 1975). Other sources cite tricyclic antidepressants as further medicines that can reduce CoQ10 status (Pelton et al 1999).
- inadequate intake or biosynthesis to meet increased requirements resulting from illness or excess physical exertion.
- genetic defects — deficiencies of CoQ10 have been associated with four major clinical phenotypes: (1) encephalomyopathy characterised by a triad of recurrent myoglobinuria, brain involvement, and ragged-red fibres; (2) infantile multisystemic disease typically with prominent nephropathy and encephalopathy; (3) cerebellar ataxia with marked cerebellar atrophy; and (4) pure myopathy (Quinzii et al 2008).

MAIN ACTIONS

Antioxidant

CoQ10 is a powerful antioxidant that buffers the potential adverse consequences of free radicals produced during oxidative phosphorylation in the inner mitochondrial membrane (Young et al 2007). It also binds to a site in the inner mitochondrial membrane that inhibits the mitochondrial permeability transition pore (MPTP).

Being a vital electron and proton carrier, CoQ10 supports adenosine triphosphate (ATP) synthesis in the mitochondrial inner membrane and stabilises cell membranes, preserving cellular integrity and function. It also reconstitutes vitamin E back into its antioxidant form by transforming vitamin E radicals to their reduced (active) form (Kaikkonen et al 2002).

Clinical note — Improving bioavailability

Absorption of compounds from the gastrointestinal tract is one of the important determinants of oral bioavailability. The absorption of oral CoQ10 is slow and limited due to its hydrophobicity and large molecular weight (Ochiai et al 2007). Research indicates that intestinal absorption of CoQ10 is enhanced when taken with food. To further improve bioavailability, specialty formulations have been produced by various manufacturers. Ochiai et al report that an emulsified form of CoQ10 had superior intestinal absorption and achieved a higher peak concentration than for a suspension formulation. Zmitek et al found that the water solubility and bioavailability of CoQ10 was increased significantly with the use of an inclusion complex with beta-cyclodextrin (Zmitek et al 2008). This complex is widely used as Q10Vital in the food industry. PureSorb-Q40 (water-soluble type CoQ10 powder) is reported in single-dose human and rat studies to have a greater absorption rate and absorbed volume of CoQ10, even taken postprandially, than those of regular CoQ10, which is lipid-soluble and generally taken in the form of soft gel capsules (Nuku et al 2007). Ullmann et al tested the bioavailability of DSM Nutritional Products Ltd (Kaiseraugst, Switzerland). CoQ10 10% TG/P (all-Q), a new tablet-grade formulation, with CoQ10 Q-Gel Softsules based on the Bio-Solv technology (Tishcon Corp., Salisbury, MD; marketed by Epic4Health, Smithtown, NY) and Q-SorB (Nature's Bounty, Bohemia, NY) (Ullmann et al 2005). They conducted a crossover study, which showed a bioequivalence between Q-Gel and all-Q, and both preparations were found to have better bioavailability properties than Q-SorB.

Recently, CoQ10 producers have synthesised ubiquinol (the reduced form of CoQ10) in an attempt to achieve better bioavailability and higher plasma concentrations with lower oral doses. Single-blind, placebo-controlled studies with healthy subjects testing single oral doses of 150 or 300 mg/day and longer term (4 weeks) oral administration of 90, 150, or 300 mg/day confirmed significant absorption of ubiquinol from the gastrointestinal tract (Hosoe et al 2007). Additionally, no safety concerns were noted on standard laboratory tests for safety or on assessment of adverse events for doses of up to 300 mg for up to 2 weeks after treatment completion.

Cardioprotective

CoQ10 supplementation offers myocardial protection during cardiac surgery, as indicated by clinical trials that observed improved postoperative cardiac function and reduced myocardial structural damage with presurgery administration of CoQ10. Studies with animal models have found that CoQ10 improves preservation of mitochondrial ATP-generating capacity after ischaemia and reperfusion (Pepe et al 2007). Treated animals demonstrate improved myocardial contractile function, increased coronary flow, reduced release of creatine kinase and malondialdehyde in the cardiac effluent.

Doxorubicin — induced cardiotoxicity

Irreversible oxidative damage to cardiac mitochondria is believed to account for the dose-related cardiomyopathy induced by anthracyclines. Tests in animal models have demonstrated that CoQ10 protects against doxorubicin cardiotoxicity, possibly via antioxidant activity and protection of mitochondrial function (Combs et al 1977, Folkers et al 1978). Clinical studies provide some support for the use of oral CoQ10 and indicate that adjunctive treatment provides protection against cardiotoxicity or liver toxicity during cancer therapy; however, further studies are required to prove this association conclusively (Roffe et al 2004).

Antihypertensive

In the 1970s, Yamagami et al observed a deficiency in CoQ10 in patients with hypertension (Yamagami et al 1975, 1976) and suggested that correction of the deficiency could result in hypertensive effects. Small studies were initially conducted with hypertensive patients identified as CoQ10 deficient.

Since then, numerous studies have been conducted. In 2007, a meta-analysis was published which evaluated 12 clinical trials (n = 362) and found that oral CoQ10 has the potential in hypertensive patients to lower systolic blood pressure by up to 17 mmHg and diastolic blood pressure by up to 10 mmHg without significant side effects (Rosenfeldt et al 2007). Interestingly, most trials fail to identify the subjects' baseline CoQ10 plasma levels and determine whether oral administration restored levels to within the normal range. It has been suggested that CoQ10 supplementation is associated with a decrease in total peripheral resistance, possibly because of action as an antagonist of vascular superoxide, either scavenging or suppressing its synthesis (McCarty 1999).

Immunostimulant activity

Several models of immune function have demonstrated the immunostimulant activity of CoQ10 (Folkers & Wolaniuk 1985).

Endothelial function

A randomised study involving 40 dyslipidaemic patients with type 2 diabetes mellitus found that oral CoQ10 (200 mg daily) taken over 12 weeks improved the endothelial function of conduit arteries of the peripheral circulation (Watts et al 2002). Another study of 80 subjects using the same dose for the same treatment period failed to improve endothelial forearm vasodilator function when given alone, although when combined with fenofibrate, the effectiveness was significant (Playford

et al 2003). Both research groups suggested that the effect may be due to an increase in the bioactivity of and/or responses to endothelium-derived relaxing factors, including nitric oxide.

Neuroprotective

Oxidative stress, resulting in glutathione loss and oxidative DNA and protein damage, has been implicated in many neurodegenerative disorders, including Alzheimer's disease, Parkinson's disease and Huntington's disease (Young et al 2007). Experimental studies in animal models suggest that CoQ10 may protect against neuronal damage that is produced by ischaemia, atherosclerosis and toxic injury. Though most have tended to be pilot studies, there are published preliminary clinical trials showing that CoQ10 may offer promise in many brain disorders.

Regulates genomic expression

CoQ10 targets the expression of multiple genes, especially those involved in cell signalling and intermediary metabolism (Pepe et al 2007).

OTHER ACTIONS

Recent research has identified that CoQ10 affects the expression of genes involved in human cell signalling, metabolism and transport (Groneberg et al 2005). This mechanism may account for some of the pharmacological effects observed with CoQ10 supplementation. Additionally, CoQ10 inhibits the formation of beta-amyloid protein in vitro (Ono et al 2005). CoQ10 affects the transport activity of P-gp, although the clinical significance of this remains to be established (Itagaki et al 2008).

CLINICAL USE

Cardiovascular diseases

In 1972, Folkers and Littaru from Italy documented a deficiency of CoQ10 in human heart disease (Ernster & Dallner 1995).

Since those early reports, a steady stream of research articles has been published and clinical experience in its use as an adjunct to conventional treatment in various forms of heart disease has accumulated. Data from laboratory studies have also accumulated and generally provide a supportive basis for its use.

A review by Langsjoen and Langsjoen of over 34 controlled studies and additional open studies concluded that CoQ10 supplementation goes beyond the correction of a simple deficiency state with strong evidence to show that it has the potential to reduce the risk of cardiovascular disease by the maintenance of optimal cellular and mitochondrial function in cardiomyocytes.

Although investigation into specific cardiovascular diseases has been undertaken, the results of an open study of 424 patients suggested that CoQ10 may have widespread benefits. The study found that CoQ10 supplementation produced clinically significant improvements in cardiac function and reduced medication requirements in patients with a range of cardiovascular disorders, including ischaemic cardiomyopathy, dilated cardiomyopathy, primary diastolic dysfunction, hypertension, mitral valve prolapse and valvular heart disease (Langsjoen et al 1994a).

A recent review by Langsjoen & Langsjoen (1999) of more than 34 controlled studies and additional open studies concluded that CoQ10 supplementation goes beyond the correction of a simple deficiency state, with strong evidence to show that it has the potential to reduce the risk of cardiovascular disease by the maintenance of optimal cellular and mitochondrial function in cardiomyocytes.

Congestive heart failure

CoQ10 has been reported to improve symptoms of congestive heart failure (CHF) and quality of life (QOL), and to reduce hospitalisation, and is used as standard therapy for CHF in some parts of Europe, Russia and Japan.

At the cellular level, oxidative stress, mitochondrial dysfunction and energy starvation are believed to play important roles in the aetiology of CHF (Overvad et al 1999). As such, it has been suggested that low CoQ10 levels identified in patients with CHF may play a role in disease development (Jeejeebhoy et al 2002) and that restoring myocyte nutrition with vitamin supplementation, including CoQ10, produces significant improvement (Sole & Jeejeebhoy 2002). Furthermore, an inverse relationship has been found between the severity of CHF and CoQ10 levels in blood from endocardial biopsies.

Clinical studies

CoQ10 improves systolic function in patients with heart failure as shown by a statistically significant change in ejection fraction (EF), cardiac output and stroke index compared to placebo according to the most recent meta-analysis (Sander et al 2006). The primary outcome measure was EF and secondary outcome measures were cardiac output (CO), cardiac index (CI), stroke volume (SV) and stroke index (SI). The analyses used data from 11 eligible trials (randomised, double-blind, placebo-controlled) and CoQ10 doses ranged from 60 to 200 mg/day with treatment periods ranging from 1 to 6 months. Overall, there was a significant 3.7% net improvement in EF ($P < 0.00001$). Interestingly, more profound effects on EF were observed for patients not receiving angiotensin-converting enzyme inhibitors (6.74% net improvement). To put the degree of EF improvement into perspective, the beta-blocker drug, metoprolol, is associated with an average increase in EF of 7.4% (range 3%–16%), whereas carvedilol is associated with an increase of 5% (3%–11%). CoQ10 also significantly increased the cardiac output by an average of 0.28 L/min. When a less conservative meta-analysis model was used, cardiac index, stroke volume and stroke index were also significantly improved. Sander et al (2006) used data from clinical trials by Hofman-Bang et al 1995, Khatta et al 2000, Langsjoen et al 1985, Morisco et al 1994, Munkholm et al 1999, Permanetter et al 1992, Watson et al 1999, Keogh et al 2003, Serra et al 1991, Pogessi et al 1991, Judy et al 1986.

This adds weight to the previous findings of a meta-analysis of eight RCTs which showed that adjunctive therapy with CoQ10 leads to significant improvements in total work capacity, cardiac index, cardiac output and stroke volume (Soja & Mortensen 1997). The subjects had cardiomyopathy and CHF of varying aetiologies (idiopathic, dilated, ischaemia, hypertension, valvular heart disease and congenital heart disease).

The largest controlled trial in adult cardiomyopathy and CHF was reported in 1993 (Morisco et al 1993) and involved 641 patients with New York Heart Association (NYHA) classes III and IV. The double-blind, placebo-controlled study used a dose of 2 mg CoQ10 per kg daily over 1 year and found that active treatment significantly improved arrhythmias and episodes of pulmonary oedema, as well as reducing the number of hospitalisations and overall mortality rate. The same researchers conducted a smaller double-blind, crossover study that again produced positive results. Oral CoQ10 (150 mg/day) taken for 4 weeks significantly improved EF, stroke volume and cardiac output in chronic heart failure patients (Morisco et al 1994).

Although CoQ10 is generally studied in heart failure patients (NYHA class II and III), a double-blind, placebo-controlled, randomised study published in 2004 (Berman et al) describes its effects in end-stage heart failure among patients awaiting heart transplantation. The study of 32 subjects compared Ultrasome CoQ10 (60 mg/day) to placebo over 3 months as an adjunct to conventional therapy. Significant improvements in functional status, clinical symptoms and QOL were reported for CoQ10; however, no significant changes in the echocardiography parameters (dimensions and contractility of cardiac chambers) or atrial natriuretic factor and tumour necrosis factor (ANF and TNF) blood levels were observed.

Whilst the overall body of evidence supports the use of CoQ10 in heart failure, not every trial has produced positive results. One theory proposes that the most profound effects on myocardial function occur when supplementation is given shortly after the diagnosis of CHF and before the development of irreversible myocyte loss and fibrosis. Some commentators have suggested that the sample sizes, severity and duration of disease, treatment dose and duration of treatment may have contributed to the neutral effects observed (Langsjoen 2000). An important issue that often fails to be considered is the measurement of plasma and myocyte CoQ10 concentrations and whether supplementation has achieved levels that are within the range likely to produce clinical results.

More recently, Langsjoen and Langsjoen (2008) reported that patients with CHF, NYHA class IV, often fail to achieve adequate plasma CoQ10 levels on supplemental ubiquinone at dosages up to 900 mg/day. These patients often have plasma total CoQ10 levels of less than 2.5 microgram/mL and limited clinical improvement. One theory proposed to explain this discrepancy is that critically ill patients have intestinal oedema, which may reduce oral CoQ10 absorption. To test this hypothesis, seven patients with advanced CHF were identified (mean EF 22%) with subtherapeutic plasma CoQ10 levels with mean level of 1.6 microgram/mL on an average dose of 450 mg of ubiquinone daily (150–600 mg/day) (Langsjoen & Langsjoen 2008). The doses of all patients were increased by an average of 580 mg/day of ubiquinol (450–900 mg/day) with follow-up plasma CoQ10 levels, clinical status and EF measurements by echocardiography. At these higher doses, mean plasma CoQ10 levels increased from 1.6 microgram/mL (0.9–2.0 microgram/mL) up to 6.5 microgram/mL (2.6–9.3 microgram/mL) with a subsequent mean improvement in EF from 22% (10–35%) to 39% (10–60%). Substantial clinical improvements were also reported with higher dosing as patients' NYHA class improving from a mean of IV to a mean of II (I–III).

Hypertension and cholesterol lowering

CoQ10 has been studied both as stand-alone and adjunctive treatment in hypertension. In 2007, a meta-analysis was published which evaluated 12 clinical trials (n = 362) consisting of 3 randomised controlled trials, 1 crossover study and 8 open label studies (Rosenfeldt et al 2007). In the randomised controlled trials (n = 120), systolic blood pressure in the treatment group decreased by 16.6 mmHg (12.6–20.6, $P < 0.001$), with no significant change in the placebo group. Diastolic blood pressure in the treatment group was also significantly reduced after treatment by 8.2 mmHg (6.2–10.2, $P < 0.001$), with no significant change in the placebo group. In the crossover study (n = 18), systolic blood pressure decreased by 11 mmHg and diastolic blood pressure by 8 mmHg with no significant change in the placebo group. In the open label studies (n = 214), mean systolic blood pressure decreased by 13.5 mmHg (9.8–17.1, $P < 0.001$) with active treatment and mean diastolic blood pressure significantly decreased by 10.3 mmHg (8.4–12.3, $P < 0.001$).

Previously, a review of eight studies concluded that supplemental CoQ10 results in a mean decrease in systolic blood pressure of 16 mmHg and in diastolic blood pressure of 10 mmHg (Rosenfeldt et al 2003). The effect on blood pressure has been reported within 10 weeks of treatment at doses usually starting at 100 mg daily. One small 10-week open study of 26 subjects with essential hypertension study found that an oral dose of 50 mg taken twice daily also reduced total serum cholesterol levels with a modest increase in serum HDL cholesterol (Digiesi et al 1994).

Cardiac surgery

The use of CoQ10 supplementation before cardiac surgery has been studied since the early 1980s. Since that time, growing evidence suggests that CoQ10 can reduce reperfusion injury after coronary artery bypass surgery, reduce surgical complications, accelerate recovery times and, possibly, shorten hospital stays (Chello et al 1996, Chen et al 1994, Judy et al 1993, Rosenfeldt et al 2002, Taggart et al 1996, Tanaka et al 1982, Zhou et al 1999). In general, the studies that achieved positive results had provided supplements for 1–2 weeks prior to surgery.

One study observed that continuing to administer CoQ10 for 30 days after surgery hastened the recovery course to 3–5 days without complications, compared with a 15–30-day recovery period for a control group, which did experience complications (Judy et al 1993, Rosenfeldt et al 2002).

The most recent randomised, double-blind trial investigated the effects of preoperative high-dose CoQ10 therapy (300 mg/day) in patients undergoing elective cardiac surgery (mainly coronary artery bypass graft surgery or valve replacement) (Rosenfeldt et al 2005). Approximately 2 weeks of active treatment resulted in significantly increased CoQ10 levels in the serum, atrial myocardium and mitochondria compared with placebo, but no significant change in the duration of hospital stay. Active treatment also improved subjective assessment of physical QOL (+13%) compared with placebo; however, the authors point out that physical QOL does not necessarily indicate improved cardiac pump function and further studies are required with larger sample sizes to clarify the role of CoQ10 in cardiac surgery.

The use of CoQ10 as preoperative treatment may hold special significance for older patients, who generally experience poorer recovery of cardiac function after cardiac surgery than their younger counterparts. One explanation gaining support is that the aged myocardium has less homeostatic reserve and so is more sensitive to both aerobic and physical stress and less well equipped to deal with cardiac surgery. Two studies have confirmed this theory, demonstrating an age-related deficit in myocardial performance after aerobic and ischaemic stress and the capacity of CoQ10 treatment to correct age-specific diminished recovery of function (Rosenfeldt et al 1999).

Besides improving cardiac resilience, CoQ10 has been found to reduce skeletal muscle reperfusion injury after clamping and declamping by reducing the degree of peroxidative damage (Chello et al 1996).

Angina pectoris

Based on the observation of relative CoQ10 deficiency in patients with ischaemic heart disease, and in animal models showing that it prevents reperfusion injury, several randomised clinical trials have been performed in angina pectoris. The doses used have varied from 60 mg to 600 mg daily, and the time frames for use varied from 4 days to 4 weeks. Overall, CoQ10 appears to delay signs of oxygen deficiency in the myocardium, increases patients' stamina on a treadmill or during exercise and delays the onset of angina (Overvad et al 1999), as well as reducing glyceryl trinitrate consumption (Kamikawa et al 1985).

Statin drug use

The mechanism of action of the statin group of drugs is inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, an enzyme involved in the biosynthesis of cholesterol from acetyl-CoA. Inhibition of this enzyme also adversely affects the intrinsic biosynthesis of CoQ10, as demonstrated in laboratory animals and humans and reduces plasma and myocardial levels of CoQ10 (Bargossi et al 1994b, Folkers et al 1990, Rosenfeldt et al 2005).

This fact, plus the role of CoQ10 in mitochondrial energy production, which is required in muscle function, has prompted the hypothesis that statin-induced CoQ10 deficiency is involved in the pathogenesis of statin myopathy and long-term statin use may actually impair cardiac function.

At least nine observational studies and six randomised controlled trials have demonstrated that statins reduce plasma/serum levels of CoQ10 by 16–54% (Marcoff & Thompson 2007). This could be related to the fact that statins lower plasma LDL levels, and CoQ10 is mainly transported in LDL; however, a decrease is also found in platelets and in lymphocytes of statin-treated patients and, therefore, it could truly depend on inhibition of CoQ10 synthesis (Littarru & Langsjoen 2007).

Reduced muscle CoQ10 concentrations are of greater concern because they may be associated with impaired cardiac function and, theoretically, increased risk of myopathy. The results obtained by Folkers et al (1990), Silver et al (2004) and Paiva et al (2005) provide support for an association between statin use and reduced intramuscular CoQ10 levels, whereas other studies find no change to intramuscular CoQ10 concentrations (Laaksonen et al 1994, 1995a, 1996), increased risk of cardiovascular disease or impaired left ventricular systolic or diastolic function in hypercholesterolaemic subjects (Colquhoun et al 2005, Stocker et al 2006). Further investigation is required to determine whether long-term reductions of CoQ10 as a result of chronic statin therapy increase the risk of myopathy and whether subpopulations at risk, such as patients with familial hypercholesterolaemia, heart failure, or who are over 65 years of age, may benefit from CoQ10 supplementation (Levy & Kohlhaas 2006).

Whilst myopathy is considered a relatively rare side effect of statin therapy, headache is more common. An association between headache and CoQ10 deficiency was identified in a recent study which found that CoQ10 supplementation significantly improved headache disability and headache frequency (Hershey et al 2007). Whether the observed headache side effect reported with statin use would respond to CoQ10 treatment is speculative and deserves further investigation.

Anecdotally, there are reports of fatigue and general malaise with statin use which respond to CoQ10 supplementation. Controlled trials are unavailable to determine the significance of these observations; however, a case study by Walravens et al (1989) illustrates the point.

A 48-year-old physician was taking lovastatin 20 mg/day for moderate hypercholesterolaemia and he also jogged three times a week, with occasional high-altitude cycling. After 2–3 weeks of lovastatin treatment, exercise became difficult because of muscle soreness and fatigue and at 7 weeks he had severe cramps while cycling. Soreness and weakness continued for 6 months, after which he began

taking CoQ10 (30 mg daily). After a few days' treatment, muscle fatigue after exercise ceased and the severe cramps did not recur. Restarting lovastatin 10 mg 5–6 times weekly did not result in muscle cramping while CoQ10 was taken.

Currently, it is still not clear whether CoQ10 supplementation should be considered a necessary adjunct to all patients taking statin drugs; however, there are no known risks to this supplement and there is some anecdotal and clinical trial evidence of its effectiveness (Marcoff & Thompson 2007). Consequently, CoQ10 can be tested in patients requiring statin treatment, who develop statin myalgia, and who cannot be satisfactorily treated with other agents and also in those patients considered at risk of deficiency, in particular, patients with a family history of heart failure, elevated cholesterol levels and who are over 65 years of age and taking statin drugs long-term (Levy & Kohlhaas 2006). A trial of therapy may also be worthwhile in patients reporting fatigue, malaise and headaches as side effects to statin treatment.

Arrhythmias

A small open study of 27 volunteers showed that CoQ10 exerts antiarrhythmic effects in some individuals (Fujioka et al 1983).

Sports supplement/ergogenic aid

Because CoQ10 is essential for energy metabolism, researchers have speculated that it may improve athletic performance. Nine clinical studies investigating the effects of CoQ10 supplementation on physical capacity were located, generally showing negative results (Bonetti et al 2000, Braun et al 1991, Laaksonen et al 1995b, Malm et al 1997, Mizuno et al 2008, Nielsen et al 1999, Porter et al 1995, Snider et al 1992, Weston et al 1997, Ylikoski et al 1997). Test doses of CoQ10 varied from 60 mg to 150 mg daily over time periods of 28 days to 8 weeks. Of these eight studies, only two studies produced positive results. One was a double-blind, crossover trial which produced positive results on both objective and subjective parameters of physical performance (Ylikoski et al 1997). In that study 94% of athletes felt that CoQ10 had improved their performance and recovery times, compared with the 33% receiving placebo. Most recently, another double-blind, placebo-controlled, crossover study of healthy people found that oral CoQ10 (300 mg/day) taken for 8 days improved subjective fatigue sensation and physical performance during fatigue-inducing workload trials (Mizuno et al 2008).

Of the others, one study found that 150 mg CoQ10 taken over 2 months had no effect on maximal oxygen consumption, lactate thresholds or forearm blood flow, although it did improve the subjective perceived level of vigour (Porter et al 1995). Another study demonstrated that CoQ10 did not alter physiological or metabolic parameters measured as part of cardiopulmonary exercise testing; however, it did extend the time and the workload required to reach muscular exhaustion (Bonetti et al 2000). Five further clinical trials produced negative results.

One retrospective study found that muscle CoQ10 levels were positively related to exercise capacity and/or marathon performance, suggesting that runners with the highest levels performed better than those with lower levels (Karlsson et al 1996).

Postpolio syndrome

One randomised, double-blind study tested whether adding oral CoQ10 to resistance training would further improve muscle strength and endurance as well as functional capacity and health-related quality of life (Skough et al 2008). All 14 patients (8 women and 6 men) with postpolio syndrome in the 12-week study undertook muscular resistance training 3 days/week and were randomised to receive either CoQ10, 200 mg/day, or placebo. For all patients, muscle strength, muscle endurance and quality of life regarding mental health increased statistically significantly but there was no significant difference between the CoQ10 and placebo groups.

Chronic obstructive pulmonary disease (COPD)

At least two clinical trials have investigated the use of CoQ10 supplementation in COPD (Fujimoto et al 1993, Satta et al 1991). In one study, 20 patients with COPD were randomly assigned CoQ10 (50 mg) or placebo as part of their pulmonary rehabilitation program (Satta et al 1991). Treatment resulted in a 13% increase in maximum oxygen consumption and a 10% increase in maximum expired volume — both significant improvements. A dose of CoQ10 (90 mg) daily over 8 weeks was studied in a smaller trial of patients with COPD (Fujimoto et al 1993). Significantly elevated serum CoQ10 levels were associated with improved hypoxaemia at rest, but pulmonary function was unchanged.

Cystic fibrosis

Pancreatic insufficiency and a diminished bile acid pool cause malabsorption of important essential nutrients and other dietary components in cystic fibrosis (CF) (Papas et al 2008). Of particular significance is the malabsorption of fat-soluble antioxidants such as carotenoids, tocopherols and CoQ10. Despite supplementation, CF patients are often deficient in these compounds, resulting in increased oxidative stress, which may contribute to adverse health effects. Papas et al conducted a pilot study to evaluate the safety of a novel micellar formulation (CF-1) of fat-soluble nutrients and antioxidants, which included CoQ10 (30 mg/10 mL), alpha-tocopherol (200 IU), beta-carotene (30 mg), gamma tocopherol (94 mg), vitamin D3 (400 IU) and other tocopherols (31 mg). Ten CF subjects aged 8–45 years were given 10 mL of the formulation orally daily for 56 days after a 21-day washout period in which subjects stopped supplemental vitamin use except for a standard multivitamin. No serious adverse effects, laboratory abnormalities or elevated nutrient levels (above normal) were identified for the treatment. Supplementation with CF-1 significantly increased CoQ10, beta-carotene and gamma tocopherol from baseline in all subjects and improvements in antioxidant plasma levels were associated with reductions in airway inflammation in CF patients.

Periodontal disease

CoQ10 is used both topically and internally for the treatment of chronic periodontal disease. Topical application has been shown to improve adult periodontitis (Hanioka et al 1994) and a small open study has shown that oral CoQ10 supplementation can produce dramatic results within 5–7 days, making location of baseline biopsy sites impossible (Wilkinson et al 1975).

Parkinson's disease

Parkinson's disease (PD) is a neurodegenerative disorder characterised by progressive loss of dopaminergic neurons within the substantia nigra pars compacta. The pathogenesis of PD remains obscure, but there is increasing experimental and clinical data which points to a defect of the mitochondrial respiratory chain, oxidative damage and inflammation as major pathogenetic factors in PD, inducing degeneration of nigrostriatal dopaminergic neurons (Beal 2003, Ebadi et al 2001, Gotz et al 2000, Storch 2007).

It has been theorised that restoration of mitochondrial respiration and reduction of oxidative stress by CoQ10 could induce neuroprotective effects against the dopaminergic cell death in PD and could also enhance dopaminergic dysfunction (Storch 2007). As a result, CoQ10 might exert both neuroprotective and symptomatic effects in PD. Current data from controlled clinical trials are not sufficient to answer conclusively whether CoQ10 is neuroprotective in PD or has significant symptomatic effects, as results are inconsistent. The data are presented here.

A number of preclinical studies using in vitro and in vivo models of PD have demonstrated that CoQ10 can protect the nigrostriatal dopaminergic system, and levels of CoQ10 have been reported to be decreased in blood and platelet mitochondria from subjects with PD (Shults 2005). As a result, a multicentre study was conducted to determine whether CoQ10 supplementation would exert beneficial effects in the disease.

The randomised, placebo-controlled, double-blind study compared three different doses of CoQ10 (300 mg, 600 mg or 1200 mg) with placebo in 80 subjects with early PD. After 9 months of treatment, subjects taking 1200 mg CoQ10 daily experienced significant improvements in disability compared with the placebo group. CoQ10 was also well tolerated at the dosages studied (Shults et al 2002). In 2003, results were published of a double-blind, placebo-controlled study, which showed that even a relatively low dose CoQ10 (360 mg/day) taken for a short period (4 weeks) produced a significant mild benefit on PD symptoms and significantly improved visual function compared with placebo (Muller et al 2003).

The safety and tolerability of high-dose CoQ10 in subjects with PD was investigated in an open study of 17 patients (Shults et al 2004). The study used an escalating dosage of 1200, 1800, 2400 and 3000 mg/day administered together with vitamin E (alpha-tocopherol) 1200 IU/d and failed to identify any serious adverse effects with CoQ10 administration. It also identified that plasma CoQ10 levels reached a plateau at 2400 mg/day, suggesting that higher treatment doses are not required.

In 2007, a multicentre, randomised, double-blind, placebo-controlled, stratified, parallel-group, single-dose trial was conducted which used nanoparticular CoQ10, as it has been shown to provide symptomatic effects in patients with mid-stage PD without motor fluctuations (Storch et al 2007). The study of 131 volunteers with PD without motor fluctuations and a stable antiparkinsonian treatment were randomly assigned to receive placebo or nanoparticular CoQ10 (100 mg 3 times a day) for a treatment period of 3 months. This form and dose of CoQ10 led to plasma levels similar to 1200 mg/d of standard formulations. No significant changes to the Unified Parkinson's Disease Rating Scale (UPDRS) were observed with CoQ10 after stratification for L-dopa dosing.

Alzheimer's dementia

Similar to Parkinson's disease, mitochondrial dysfunction and oxidative damage appear to play a role in the pathogenesis of Alzheimer's dementia and, therefore, CoQ10 supplementation has been investigated as a possible treatment. Currently, evidence is limited to test tube and animal studies and is far from definitive.

Recently, CoQ10 was shown to inhibit beta-amyloid formation in vitro (Ono et al 2005) and protect against brain mitochondrial dysfunction induced by a neurotoxic beta-peptide in a study using brain mitochondria isolated from diabetic rats (Moreira et al 2005). McDonald et al (2005) conducted two studies with test animals and found that supplemental CoQ10 (123 mg/kg/day) taken with alpha-tocopherol acetate (200 mg/kg/day) improved age-related learning deficits; however, supplementation of CoQ10 alone at this dose, or higher doses of 250 or 500 mg/kg/day, failed to produce comparable effects.

Haemodialysis

Increased oxidative stress is associated with various complications in haemodialysis (HD) patients (Sakata et al 2008). Due to its antioxidant activity, CoQ10 was administered for 6 months to 36 HD patients. Treatment was found to partially reduce oxidative stress as measured by a decrease of oxygen radical absorbing capacity (ORAC) and Trolox equivalent antioxidant capacity (TEAC).

Migraine

An open-labelled trial investigated the effects of oral CoQ10 supplementation (150 mg/day) over 3 months in 32 volunteers with a history of episodic migraine with or without aura. CoQ10 significantly reduced both the frequency of attacks and the number of days with migraine after 3 months' treatment (Rozen et al 2002). In 2005, Sandor et al investigated the effects of CoQ10 (300 mg/day) taken over 3 months in 42 migraine subjects in a double-blind, randomised, placebo-controlled study; 47.6% of CoQ10-treated patients responded to treatment compared with 14.4% for placebo, experiencing

a (50% or less) reduction in migraine frequency (number needed to treat, 3). Active treatment was superior to placebo for reducing attack frequency, headache days and days with nausea in the third treatment month and was well tolerated.

In 2007, Hershey et al assessed 1550 paediatric patients (mean age 13.3 ± 3.5, range 3–22 yrs) attending a tertiary care centre with frequent headaches for CoQ10 deficiency (Hershey et al 2007). Of these patients, 32.9% were below the reference range. Patients with low CoQ10 were recommended to start 1 to 3 mg/kg/day of CoQ10 in liquid gel capsule formulation as part of their multidisciplinary treatment plan. Those patients who returned for follow-up (mean, 97 days) demonstrated significantly increased total CoQ10 levels and significant improvements for headache disability and headache frequency (19.2 ± 10.0 to 12.5 ± 10.8).

OTHER USES

Cancer

Currently, controlled studies are not available to determine the clinical effectiveness of CoQ10 in cancer; however, there have been several case reports of CoQ10 (390 mg/day) successfully reducing metastases or eliminating tumours entirely (Lockwood et al 1994, 1995). An in vivo study found that CoQ10 enhances the effects of immunochemotherapy (Kokawa et al 1983).

Reducing cardiotoxic effects of anthracyclines

There is some evidence that CoQ10 supplementation protects the mitochondria of the heart from anthracycline-induced damage. A systematic review of six studies (three randomised), in which patients in five of the six studies received anthracyclines, concluded that CoQ10 provides some protection against cardiotoxicity or liver toxicity during cancer treatment; however, weaknesses in design and reporting made it difficult to reach a definitive conclusion (Roffe et al 2004). Despite the high level of heterogeneity, it appeared that CoQ10 had a stabilising effect on the heart. Importantly, CoQ10 was not shown to interfere with standard treatments in the clinical trials reviewed and no adverse effects were reported in any single study for CoQ10 administration.

Sample sizes in the studies ranged from 19 to 88 patients and one study included children. The methods researchers used to measure patient tolerance to anthracyclines and other cancer treatments were heart function and toxicity in five studies and hair loss and liver enzymes in one study. The dose of CoQ10 investigated in the trials ranged from 90 mg/day to 240 mg/day.

Mitochondrial myopathy

An open multicentre study involving 44 volunteers with mitochondrial myopathies showed that treatment with CoQ10 (2 mg/kg daily) over 6 months decreased postexercise lactate levels by at least 25% in 16 patients. Of those responding, a further 3 months' treatment with either CoQ10 or placebo produced no significant differences (Bresolin et al 1990).

Age-related macular degeneration (in combination)

Mitochondrial dysfunction is likely to play a role in the pathophysiology of age-related macular degeneration (Littarru & Tiano 2005). As a result, researchers are starting to investigate therapeutic agents, such as CoQ10, which affect mitochondrial function.

Metabolic therapy consisting of a combination of omega-3 fatty acids, CoQ10 and acetyl-L-carnitine may have potential benefits as a treatment for early age-related macular degeneration by improving mitochondrial dysfunction, specifically improving lipid metabolism and ATP production in the retinal pigment epithelium, improving photoreceptor turnover and reducing generation of reactive oxygen species (Feher et al 2007). According to a pilot study and a randomised, placebo-controlled, double-blind clinical trial, both central visual field and visual acuity slightly improved after 3–6 months of treatment with the metabolic combination; however, the difference was statistically significant as compared to the base line or to controls. Treatment produced an improvement in fundus alterations as the drusen-covered area decreased significantly compared to base line readings or controls, and was most marked in the less affected eyes. Interestingly, a prospective case study on long-term treatment confirmed these observations. Visual function remained stable and, generally, drusen regression continued for years and for some intermediate and advanced cases, significant regression of drusen was found with treatment.

Friedreich's ataxia

Decreased mitochondrial respiratory chain function and increased oxidative stress and iron accumulation play significant roles in the disease mechanism of Friedreich's ataxia (FRDA), raising the possibility that energy enhancement and antioxidant therapies may be an effective treatment (Cooper & Schapira 2007). Therapeutic avenues for patients with FRDA are beginning to be explored, in particular, targeting antioxidant protection, enhancement of mitochondrial oxidative phosphorylation and iron chelation. The use of quinone therapy (ubiquinone and idebenone) has been the most extensively studied to date with clear benefits demonstrated using evaluations of both disease biomarkers and clinical symptoms (Mariotti et al 2003).

A 4-year follow-up on 10 Friedreich's Ataxia patients treated with CoQ10 (400 mg/day) and vitamin E (2100 IU/d) showed a substantial improvement in cardiac and skeletal muscle bioenergetics and heart function which was maintained over the test period and some clinical feature of disease (Hart et al 2005). Comparison with cross-sectional data from 77 patients with FRDA indicated the changes in total International Cooperative Ataxia Rating Scale and kinetic scores over the trial period were better than predicted for seven patients, but the posture and gait and hand dexterity scores progressed as predicted.

Tinnitus
In patients with a low plasma CoQ10 concentration, CoQ10 supply may decrease the tinnitus expression in chronic tinnitus aurium according to a 16-week prospective, non-randomised clinical trial (n = 20) (Khan et al 2007). CoQ10 was tested in this population because of its antioxidant activity.

Myelodysplastic syndromes
The myelodysplastic syndromes (MDS) are a collection of haematopoietic disorders with varying degrees of mono- to trilineage cytopenias and bone marrow dysplasia. In recent years, much progress has been made in the treatment of MDS and there are now several therapeutic compounds used with varying levels of success; however, side effects make them unattractive for patients (Galili et al 2007).

Galili et al tested CoQ10 supplementation in MDS patients with low to intermediate-2 risk disease. A variety of responses were observed in seven of 29 patients. Sequencing mitochondrial DNA (mtDNA) from pretreatment bone marrows showed multiple mutations, some resulting in amino acid changes, in 3/5 non-responders, 1/4 responders and in two control samples. Based on these observations, it appears that CoQ10 may be of clinical benefit in a subset of MDS patients, but responders cannot be easily preselected on the basis of either the conventional clinical and pathologic characteristics or mtDNA mutations.

Huntington's chorea
A randomised, double-blind study involving 347 patients with early Huntington's chorea showed that a dose of CoQ10 (600 mg/day) taken over 30 months produced a trend towards slow decline as well as beneficial trends in some secondary measures; however, changes were not significant at this dosage level (Huntington's Study Group 2001).

DOSAGE RANGE

According to clinical studies
- Generally 100–150 mg/day has been used for conditions such as congestive cardiac failure (Mortensen et al 1990), hypertension, neurological disease, performance enhancement, periodontal disease (Wilkinson et al 1975).
- As preparation for cardiac surgery: 100–300 mg/day for 2 weeks before surgery followed by 100 mg/day for 1 month after surgery has been used (Judy et al 1993, Rosenfeldt et al 2002, 2005).
- Angina pectoris: 60–600 mg daily.
- Chronic obstructive pulmonary disease: 50–90 mg daily.
- Congestive heart failure: 60–200 mg/day.
- Huntington's chorea: 600 mg daily.
- Migraine: 150–300 mg daily.
- Parkinson's disease (< 1200 mg/day) (Shults et al 2002) (efficacy uncertain)
- Adjunct to chemotherapy (anthracyclines) 90–240 mg/day but evidence is not definitive.

ADVERSE REACTIONS
CoQ10 appears relatively safe and non-toxic and is extremely well tolerated. Dizziness, nausea, epigastric discomfort, anorexia, diarrhoea, photophobia, irritability and skin rash occur in less than 1% of patients. This tends to occur with higher doses (> 200 mg/day).

SIGNIFICANT INTERACTIONS
When controlled studies are not available, interactions are based on evidence of pharmacological activity, case reports and other evidence and are largely theoretical.

Beta-adrenergic antagonists
Induces CoQ10 depletion — beneficial interaction with co-administration (Stargrove et al 2008).

Doxorubicin
Tests in animal models have demonstrated that CoQ10 protects against doxorubicin cardiotoxicity (Combs et al 1977, Folkers et al 1978) and clinical studies provide some support for the use of oral CoQ10 and indicate that adjunctive treatment provides some protection against cardiotoxicity or liver toxicity during cancer therapy; however, further studies are required to prove this association conclusively (Roffe et al 2004); furthermore, in vivo results indicate that CoQ10 has no significant effect on the pharmacokinetics of doxorubicin and the formation of the cytotoxic metabolite, doxorubicinol (Combs et al 1977, Zhou & Chowbay 2002) — potentially beneficial interaction with co-administration under professional supervision.

Phenothiazines
CoQ10 reduces adverse effect this drug class has on CoQ10-related enzymes, NADH oxidase and succinoxidase — beneficial interaction with co-administration (Stargrove et al 2008).

Statin drugs
Currently, it is still not clear whether CoQ10 supplementation should be considered a necessary adjunct to all patients taking statin drugs; however, there are no known risks to this supplement and there is some anecdotal and clinical trial evidence of its effectiveness (Marcoff & Thompson 2007). Consequently, CoQ10 can be tested in patients requiring statin treatment, who develop statin myalgia, headache, fatigue or malaise as statin-induced side effects. It may also prove useful for patients considered at risk of deficiency, in particular, patients with a family history of heart failure, elevated cholesterol levels and who are older than 65 years and taking statin drugs long-term (Levy & Kohlhaas 2006) — possible beneficial interaction with co-administration.

Sulfonylureas
CoQ10 reduces adverse effect this drug class has on CoQ10-related enzymes, NADH oxidase and low CoQ10 levels have been observed in people with diabetes — beneficial interaction with co-administration (Stargrove et al 2008).

Timolol
Eye drops — oral CoQ10 reduced the vascular side effects of timolol without affecting eye pressure (Takahashi 1989) — beneficial interaction with co-administration.

Tricyclic antidepressants
CoQ10 reduces adverse effect this drug class has on CoQ10-related enzymes, NADH-oxidase and succinoxidase — beneficial interaction with co-administration (Stargrove et al 2008).

Warfarin
There are three case reports suggesting that CoQ10 may decrease the international normalised ratio (INR) in patients previously stabilised on anticoagulants (Spigset 1994b). However, a double-blind crossover study involving 24 outpatients on stable long-term warfarin found that oral CoQ10 (100 mg) daily had no significant effect on INR or warfarin levels (Engelson et al 2003). Observe patients using high CoQ10 doses and taking warfarin.

Vitamin E
Reconstitutes oxidised vitamin E to its unoxidised form — beneficial interaction with co-administration.

CONTRAINDICATIONS AND PRECAUTIONS
Insufficient reliable evidence — unknown.

PREGNANCY USE
Safety has not been scientifically established.

PRACTICE POINTS/PATIENT COUNSELLING
- CoQ10 is a safe antioxidant vitamin used in supplement form for a wide range of diseases.
  - Meta-analyses provide support for its use in congestive heart failure and hypertension.
  - Clinical evidence further supports the use of presurgical supplementation in cardiac surgery, as it improves recovery and has cardioprotective activity.
  - There is also some clinical evidence suggesting a role in migraine headache, Huntington's chorea, mitochondrial myopathy, COPD, periodontal disease, haemodialysis, Friedreich's ataxia, tinnitus, age-related macular degeneration, cystic fibrosis and reducing cardiotoxicity and liver toxicity associated with anthracyclines, although further research is required.
  - Whether CoQ10 may slow the progression of PD is unclear.
- Several common medicines, such as statins, have been found to reduce serum CoQ10 status. It is still unclear whether CoQ10 should be considered a necessary adjunct to statin drugs; however, there are no known risks to this supplement and there is some anecdotal and clinical trial evidence of its effectiveness. In particular, it may be useful in patients who develop statin myalgia, headache, fatigue or malaise and those considered at risk of deficiency.

PATIENTS' FAQs
What will this vitamin do for me?
CoQ10 is an antioxidant vitamin used in every cell of the body. It is necessary for healthy function and can improve heart function, lower blood pressure and reduce angina. Taken before cardiac surgery, it has been shown to reduce complications and hasten recovery in some studies. It may also provide benefits in migraine headache, Huntington's chorea, mitochondrial myopathy, COPD, periodontal disease, haemodialysis, Friedreich's ataxia, tinnitus, age-related macular degeneration, cystic fibrosis and reducing cardiotoxicity and liver toxicity associated with anthracyclines, although further research is required to definitively confirm effect. Whether it is helpful in PD is not clear. People taking statin drugs long term and experiencing side effects could take a trial of CoQ10 and see whether it helps them.

When will it start to work?
This depends on the indication. For heart conditions and to reduce migraine, 10–12 weeks may be required. To delay the progression of PD, one study found that effects started after 9 months' use.

Are there any safety issues?
Medical monitoring is required in patients taking warfarin and starting high-dose CoQ10 supplements; however, even high-dose supplements are well tolerated and considered safe.

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Colostrum

BACKGROUND AND RELEVANT PHARMACOKINETICS

Colostrum is the milk produced by female mammals towards the end of pregnancy and secreted from the mammary gland in the first 2 days after giving birth. It is a very complex fluid, rich in nutrients, antibodies, growth factors, vitamins and minerals (Uruakpa et al 2002). The antibodies provide passive immunity to the newborn, and the growth factors stimulate development of the gastrointestinal tract.

CHEMICAL COMPONENTS

Colostrum contains macronutrients, such as protein and carbohydrate, micronutrients, such as vitamins and minerals, together with cytokines, including IL-1-beta, IL-6, trypsin inhibitors, protease inhibitors and oligosaccharides. It also contains growth factors such as insulin-like growth factor (IGF)-I and -II, transforming growth factor-alpha and -beta, lactoferrin, epidermal growth factor and others. Several different antimicrobial factors are also present, such as immunoglobulin (Ig) A, secretory IgA, IgG-1, IgG-2 and IgM, lactoferrin, lactoperoxidase and lysozyme, which produce both specific and non-specific bacteriostatic and bacteriocidal effects on many pathological microorganisms, including bacteria, viruses and fungi. IgG-1 is the principal immunoglobulin type in colostrums, and IgM, IgA and IgG-2 are present in lower amounts (Mach & Pahud 1971).

FOOD SOURCES

Bovine colostrums (BC) are derived from cows, and hyperimmune BC is derived from cows that have been exposed to organisms that can cause disease in humans.

Clinical note — Hyperimmune bovine colostrum

Bovine colostrum contains a variety of Ig, but the specific Ig present varies and is influenced by previous immune system challenges. Hyperimmune BC, in which the concentration of specific antibodies is raised, can be produced by immunising cows with either specific pathogens or their antigens. For example, BC from cows exposed to rotavirus might contain a relatively high neutralising Ig titre against the virus (as well as many other pathogenic microorganisms), whereas BC collected from cows never exposed to rotavirus is less likely to have specific neutralising Ig against rotavirus. This is an important distinction, because much of the research on BC as prophylaxis or treatment for infectious disease has focused on products that are, as a consequence of specific immune provocation, immunologically unique (Kelly 2003).

MAIN ACTIONS

Imparts passive immunity and stimulates growth of the neonatal gastrointestinal tract

Just as the immunoglobulins of human colostrum impart passive immunity to the newborn child, so too BC provides protection against microbial infections and confers passive immunity to the newborn calf until its own immune system matures (Korhonen et al 2000). Studies with targeted hyperimmune BC suggest that passive immunity may prevent or treat infectious diseases that affect the entire length of the gastrointestinal tract (Pacyna et al 2001).

Immunomodulatory activity

An animal study found that BC has a Th1 promoting activity, which may be helpful in treating

various infectious diseases, including influenza (Biswas et al 2007, Yoshioka et al 2005). When BC was administered to weaned piglets, this intervention increased total serum IgA levels, stimulated ileal Peyer's patch and both Th1 and Th2 cytokine production (Boudry et al 2007). Further research would be needed to assess if BC increases Th1 in already high Th1 profiles or simply modulates the immune function where there is dysfunction.

In contrast, a clinical study found no significant effect on immune parameters for healthy volunteers aged 40–80 years who received BC concentrate 1.2 g/d. The researchers suggested that improving immune function in people with healthy immune responses is difficult thereby explaining why no significant effect was observed (Wolvers et al 2006).

Antibacterial and antiviral effects

Targeted hyperimmune BCs have proven effective in prophylaxis against various human infectious diseases caused by organisms such as rotavirus, *Shigella flexneri*, *Escherichia coli*, *Clostridium difficile*, *Streptococcus mutans*, *Cryptosporidium parvum* and *Helicobacter pylori* (Korhonen et al 2000). Hyperimmune BC from cows previously immunised with a vaccine of 17 strains of pathogenic diarrhoea bacteria was shown to inhibit in vitro growth of the same pathogens by destroying cell walls and agglutinating with bacteria (Xu et al 2006).

It is suspected that colostrum may modulate the interaction of *H. pylori* and other adhesin-expressing pathogens with their target tissues, chiefly due to phosphatidylethanolamine and its derivatives rather than to an antibody response (Bitzan et al 1998).

Improves gut permeability

Studies with agents known to disrupt gut permeability indicate that BC has a preventive effect that is likely to be a result of more than one growth factor present in the colostrum.

Reduces NSAID-induced intestinal damage

Defatted BC had major beneficial effects in preventing non-steroidal anti-inflammatory drug (NSAID)-induced gut injury in a variety of well-validated in vivo and in vitro models (Kim et al 2005a, 2005b, Playford et al 1999). BC improves the integrity of intestinal villi and prevents NSAID-induced increases in small intestine permeability. More specifically, the studies indicate that it stimulates both cell migration and proliferation, thereby enhancing the natural repair mechanisms that occur during acute mucosal injury. One of the studies by Kim et al (2005a) identified that when BC is administered together with glutamine, gastrointestinal protection is greater than when either agent is used alone. The other study, further, found that the overgrowth of enteric aerobic bacteria seen with NSAID administration did not occur to the same extent with BC (Kim et al 2005b).

OTHER ACTIONS

The high nutritional content of BC makes it an excellent source of many macro- and micronutrients.

Antioxidant activity

Bovine colostrum given to intestinal ischaemia/reperfusion injured rats experienced reduced oxidative stress and reduced nitric oxide (NO) overproduction in the lungs, which reduced lung injury. Superoxide dismutase and glutathione peroxidase levels were significantly increased and myeloperoxidase and malondialdehyde were significantly reduced in lung tissue indicating an overall reduction in oxidative stress (Choi et al 2007). The same research team went on to show that BC may reduce damage in brain ischaemia/reperfusion-injured rats (Choi & Ko 2008).

CLINICAL USE

The use of BC as a dietary supplement has increased substantially over the past 2 decades. Unlike other dietary supplements, the composition of BC is not precisely defined and varies greatly according to the breed and health status of the cow, feeding practices, previous exposure to infectious organisms and time collected postparturition (Kelly 2003).

Prevention and treatment of infection

Targeted hyperimmune BC products have proven effective in prophylaxis against various infectious diseases in humans.

Infectious diarrhoea

Rotavirus infection

The clinical evidence available suggests that hyperimmune BC is a promising agent in the prophylaxis and treatment of infectious diarrhoea caused by rotavirus. One Australian study using BC containing

Clinical note — Ovine colostrum and colostrum proline-rich polypeptides

There is new research appearing in the literature regarding colostrum from ewes, mostly using a product called Colostrinin™ which is a proline-rich, polypeptide complex from mammalian colostrum. In-vitro, in-vivo and clinical trials using this product have gained attention as having possible therapeutic benefit in the treatment of mild or moderate Alzheimer's disease (AD) by improving cognitive symptoms and delaying the disease process. Two mechanisms have been proposed to explain these benefits — an antioxidant mechanism which reduces oxidative stress and prevention of beta-amyloid aggregation (Bilikiewicz & Gaus 2004, Boldogh & Kruzel 2008, Stewart 2008). The anti-inflammatory action of this substance may also have an effect on decreasing IgE/IgG1 production, which could prevent or reduce allergic responses (Boldogh et al 2008). It seems that bovine colostrum proline-rich polypeptides have also displayed some potential in this anti-allergenic arena. Ovine colostrum, Colostrinin™ and colostrum proline-rich polypeptides are products to watch and would benefit from broader clinical trials to confirm their potential therapeutic uses.

high titres of antibody to all four human rotavirus serotypes found that administration successfully prevented symptomatic infection in 100% of children treated with the preparation (Davidson et al 1989). It also reduced the duration of rotavirus excretion, which may have implications for preventing cross-infection. A double-blind study of 75 boys aged 6–24 months with rotavirus diarrhoea compared ordinary BC to hyperimmune BC (100 mL three times daily for 3 days) from cows immunised with four serotypes of human rotavirus (Mitra et al 1995). Diarrhoea ceased within 48 hours in 50% of children receiving hyperimmune BC, whereas 100% of children receiving ordinary BC continued to have diarrhoea. Total stool output (g/kg) between admission and cessation of diarrhoea was also reduced in the group receiving hyperimmune BC compared with ordinary BC. Another double-blind study also found that treatment with antirotavirus immunoglobulin of BC origin is effective in the management of children with acute rotavirus diarrhoea (Sarker et al 1998). A double-blind study of children aged 6–30 months found that treatment with hyperimmune BC (100 mL solution four times daily for 4 days) leads to improved weight gain, decreased duration of diarrhoea and resulted in fewer stools, although the differences were not statistically significant compared to ordinary colostrum or placebo (Ylitalo et al 1998).

Studies using hyperimmune BC in young children have identified rotavirus antibodies as early as 8 hours after ingestion and up to 72 hours after consumption has ceased, with a strong relation between the titre of rotavirus antibody administered and the level of antibody activity detected in the faeces (Pacyna et al 2001). This suggests that passive immunity is imparted to the entire length of the gastrointestinal tract.

Shigella infection

According to one small study, hyperimmune BC with a high titre of anti-*Shigella flexneri* 2a lipopolysaccharide prevented the incidence of shigella infection in 10 of 10 volunteers, whereas 5 of 11 volunteers administered a control substance went on to develop the infection (Tacket et al 1992).

HIV-induced diarrhoea

BC has also been investigated as a potential treatment in HIV-induced diarrhoea, a symptom that occurs in most patients infected with AIDS. A BC product (Lactobin, Biotest, Dreieich, Germany) containing high titres of antibodies against a wide range of bacterial, viral and protozoal pathogens, as well as against various bacterial toxins, was tested in a multicentre pilot study involving 29 HIV-infected patients (Rump et al 1992). An oral dose of 10 g/day produced a transient (10 days) or long-lasting (>4 weeks) normalisation of the stool frequency in 21 patients. Mean daily stool frequency decreased from 7.4 to 2.2 at the end of the treatment. Some success was also obtained 1 year later in a prospective, open, uncontrolled study of 25 HIV patients with chronic refractory diarrhoea and either confirmed cryptosporidiosis (n = 7) or absence of demonstrable pathogenic organisms (n = 18) (Plettenberg et al 1993). An oral dose of 10 g/day of an immunoglobulin preparation from BC over a period of 10 days led to complete remission of cryptosporidiosis infection in three of seven subjects and two had partial remission. Complete remission was also seen in seven of 18 patients with diarrhoea and negative stool culture and a further four had partial remission. Of those subjects not responding to treatment, doubling of the dose to 20 g/day led to partial remission in four more patients and complete remission in one.

A BC product designed for slow passage through the gastrointestinal tract (ColoPlus) was tested over 4 weeks in an open-label study of 30 people with HIV-associated diarrhoea (Floren et al 2006). Treatment resulted in a dramatic decrease in daily stool evacuations (from 7.0 ± 2.7 to 1.3 ± 0.5), a mean increase of 7.3 kg of body weight, a 125% increase in $CD4^+$ count and a substantial decrease in self-estimated fatigue.

Reducing incidence of upper respiratory tract infections (URTIs)

IgA is found in saliva and acts as a major barrier preventing pathogens entering the body via the oral route. As such, the level of secretory IgA has been found to correlate with resistance to some viral infections. According to two clinical studies, BC (20 g/day) increases salivary IgA levels, a factor that could feasibly increase the host's resistance to infection (Crooks et al 2006, Mero et al 2002). In the study by Crooks et al, secretory IgA levels were elevated by 79% after 12 weeks of BC administration in athletes. The presence of numerous immune factors in BC further provides a theoretical basis for its use; however, little clinical investigation has been conducted to confirm its preventive effects.

In 2003, results of a randomised, double-blind, placebo-controlled trial were published, providing some support for its use as a prophylactic agent (Brinkworth & Buckley 2003). The study of 174 physically active young males compared colostrum powder (60 g/day; intact™, Numico Research Australia Pty Ltd) to concentrated whey powder over 8 weeks. During the test period, a significantly fewer proportion of subjects taking BC reported URTI symptoms than the control group; however, BC did not alter the duration of URTI once infection was established. Due to the self-reporting method used in this study, results should be viewed as preliminary and require further confirmation. An open study with 605 children in India achieved exceptional results as a prophylactic in preventing recurrent episodes of upper respiratory tract infections and diarrhoea. The children received a BC (Pedimune®) for 12 weeks, which reduced the incidence of URTI by 91% and diarrhoea by 86% (Patel & Rana 2006). This was an open study and more rigorous clinical trials are needed to confirm these findings.

Influenza prophylactic

A recent trial compared a colostrum supplement, given over 2 months, with an influenza vaccination and a combination of the two, for the prevention of flu. Over the next 3 months, the group

receiving colostrum treatment only had the lowest number of flu episodes (13), with the next highest in the colostrum and vaccination group (14) and then the vaccination only (41) and highest in non-treated subjects (57). The study was repeated with 65 high-risk cardiovascular patients, which once again produced positive results, as the incidence of hospital admissions and complications was higher in those who received only the vaccination compared to people receiving colostrum. Overall, colostrum supplementation was considered at least three times more effective than vaccination for flu prevention (Cesarone et al 2007).

Improved physical performance and preservation of muscle mass

BC has been used by athletes mainly as a natural source of IGF-I because it has an anabolic effect and is involved in the regulatory feedback of growth hormone. It is taken with the belief that protein catabolism will be reduced during intense training periods and physical performance will improve.

A double-blind, crossover study of nine male athletes confirmed that ingestion of BC (125 mL/day; Bioenervie, Viable Bioproducts) resulted in elevated concentrations of IGF-I; however, no significant effects were reported for serum IgG or saliva IgA concentrations (Mero et al 1997). Several years later in a larger study of athletes, under double-blind study conditions, researchers confirmed that BC ingestion produced significant increases in serum IGF-I (Mero et al 2002). The dose of 20 g/day of BC (dynamic supplement) was used during a 2-week training period in this study, which further found that saliva IgA levels increased with this particular treatment.

In a more recent trial, 29 cyclists were randomly assigned to take either 10 g/day of a BC protein concentrate or a placebo consisting of 10 g/day of whey protein during normal training over 5 weeks. Performance tests showed that BC treatment improved results in a 40 km time trial during a high-intensity training regimen and also maintained ventilatory threshold (Shing et al 2006). The same researchers also found that the supplement modulated immunity before and after training and prevented postexercise reductions in serum IgG (2) at the end of the high-intensity training period. A trend towards fewer upper respiratory tract illnesses was also detected (Shing et al 2007).

Gastrointestinal protection against NSAID-induced damage

BC has also been investigated in a small, randomised, crossover study as prophylaxis against NSAID-induced gastrointestinal damage (Playford et al 2001). A spray-dried, defatted colostrum (125 mL three times daily) was co-administered with indomethacin (50 mg three times daily) for 5 days in the first phase, then the effect of 7 days treatment with the colostral solution on gut permeability was determined in subjects taking NSAID long-term. Indomethacin (150 mg/day) caused a threefold increase in gut permeability after 5 days, whereas no change was observed when colostrum was co-administered, suggesting a protective effect. In contrast, no protective effect was seen in subjects who had been using NSAIDs long-term and then administered colostrum for 1 week.

Antidiabetic

It has been suggested that BC may have an effect on blood glucose levels. A small, randomised study of 16 patients with type 2 diabetes tested the effects of BC (10 g/day) over 4 weeks. Total cholesterol and triglyceride levels decreased significantly with active treatment, and a reduction in blood glucose levels and ketones were observed, which suggests a potential role for BC in diabetes management (Kim et al in press). Larger clinical studies are warranted to confirm this finding.

OTHER USES

Due to its effects on gut permeability, BC is used in a variety of other conditions, such as inflammatory bowel disease, coeliac disease, food allergies, intestinal infection and inflammatory joint diseases. It has also been used to restore normal gut permeability in people using chemotherapy. In some instances, it is used with glutamine for these indications.

DOSAGE RANGE

According to clinical studies

- Diarrhoea due to rotavirus: 100 mL three times daily for 3 days of BC from cows immunised with the four serotypes of human rotavirus.
- HIV-induced diarrhoea: 10 g/day (Lactobin, Biotest, Dreieich, Germany).
- Prevention of URTI: 60 g/day (intact™, Numico Research Australia Pty Ltd).
- Increasing serum IGF-I levels: 125 mL/day (Bioenervie, Viable Bioproducts) or 20 g/day (Dynamic supplement).
- Prevention of NSAID-induced gastrointestinal damage: 125 mL three times daily of spray-dried, defatted BC.
- For improving performance in high-intensity training and reducing exercise-induced URTI: 10 g/day.

TOXICITY

Not known.

ADVERSE REACTIONS

Not known.

SIGNIFICANT INTERACTIONS

Not known.

CONTRAINDICATIONS AND PRECAUTIONS

Only BC products produced under strict quality control guidelines should be used. They typically contain lactose, so should be avoided by people with lactose intolerance.

PREGNANCY USE

Likely to be safe.

PRACTICE POINTS/PATIENT COUNSELLING

- Colostrum is a very complex fluid that is rich in nutrients, antibodies, growth factors, vitamins and minerals.
- Targeted hyperimmune BC products have proven effective in prophylaxis against various infectious diseases in humans, notably infectious diarrhoea.
- BC is a popular supplement among athletes and used mainly as a natural source of IGF-I because it has an anabolic effect and is involved in the regulatory feedback of growth hormone.
- Preliminary evidence suggests that BC may prevent NSAID-induced gastrointestinal damage and improve gut permeability.
- Most studies use hyperimmune BC in which the concentration of specific antibodies is raised.
- Preliminary evidence shows some potential for BC in flu prevention and upper respiratory tract infections.

PATIENTS' FAQs

What will this supplement do for me?

Bovine colostrum contains nutrients, antibodies, growth factors, vitamins and minerals, and has a variety of effects on the gastrointestinal tract, immune function and the ability to fight some infections, and may possibly reduce muscle catabolism.

When will it start to work?

Studies with infectious diarrhoea have reported benefits within 3–4 days, and improvement in gut permeability within 5 days.

Are there any safety issues?

Bovine colostrum produced under quality control guidelines is a safe substance; however, it should be avoided by people with lactose intolerance.

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Cranberry

HISTORICAL NOTE Native American Indians used cranberries as both a food and a treatment for bladder and kidney diseases. In the mid 1800s, German scientists suggested that cranberry juice had antibacterial activity, supporting its use as a treatment for bladder infections. Recent investigation has confirmed its usefulness in the prevention of urinary tract infections.

COMMON NAME
Cranberry

OTHER NAMES
Kronsbeere, marsh apple, moosbeere, preisselbeere

BOTANICAL NAME/FAMILY
Vaccinium oxycoccus, *Vaccinium macrocarpon* (family Ericaceae)

PLANT PART USED
Fruit

CHEMICAL COMPONENTS
Catechin, flavone glycosides, fructose, organic acids, proanthocyanidins, vitamin C.

Cranberry has a high flavonol content (100–263 mg/kg) (Hakkinen et al 1999) — higher than commonly consumed fruits and vegetables.

MAIN ACTIONS

Bacteriostatic
The adhesion of pathogenic organisms to a tissue surface is required to initiate most infectious diseases (Sharon & Ofek 2002). The proanthocyanidins in cranberry are potent inhibitors of *Escherichia coli* adhesion, thereby influencing the initiation of disease without exerting bactericidal activity. One in vitro study found that cranberry juice inhibited adhesion of 46 different *E. coli* isolates by 75% (Sobota 1984): when administered to mice for 14 days, adherence of *E. coli* to uroepithelial cells was inhibited by 80%. Significant inhibition of adherence was also observed in samples of human urine 1–3 hours after subjects drank a cranberry drink.

The morphology of *E. coli* is changed when grown in the presence of cranberry juice or extract (Johnson et al 2008). It appears that the antiadhesion effects are a result of irreversible inhibition of the expression of P-fimbriae of *E. coli* (Ahuja et al 1998). Electron micrographic evidence suggests that cranberry juice acts either on the cell wall, preventing proper attachment of the fimbrial subunits, or as a genetic control preventing the expression of normal fimbrial subunits, or both (Gupta et al 2007). Furthermore, cranberry juice has been shown to disrupt bacterial ligand-uroepithelial cell receptor binding (Liu et al 2008). This inhibitory effect has been seen with *Staphylococcus aureus* (Magarinos et al 2008), *E. coli* and uroepithelial tissues, but also in the adhesion of *Helicobacter pylori* to human gastrointestinal cells (Burger et al 2002) and in the co-aggregation of oral bacteria and *Streptococcus mutans* counts in saliva (Sharon & Ofek 2002, Weiss et al 1998).

Antioxidant
Cranberries consistently rank highly among common fruits with antioxidant activity. In particular, the polyphenolic compounds in cranberry display substantial antioxidant capacity. In vitro tests with whole fruit and isolated flavonol glycosides found in cranberry showed free radical scavenging activity comparable or superior to that of vitamin E (Yan et al 2002). In vivo studies demonstrate that cranberry juice increases plasma antioxidant status (Villarreal et al 2007). A small human trial demonstrated that a single 240-mL serving of cranberry juice increased plasma antioxidant capacity significantly greater than controls receiving an equivalent amount of vitamin C in solution (Vinson et al 2008).

Increases excretion of oxalic acid and uric acid
According to an open study, a dose of 330 mL cranberry juice can increase the excretion of oxalic acid and uric acid (Kessler et al 2002).

Alterations to urinary pH
Earlier hypotheses that cranberry juice prevents UTI by acidification of urine or by its hippuric acid content have not been substantiated. Results from human studies are contradictory, but overall suggest no significant change to urinary pH at doses less than 330 mL daily. A crossover study of 27 patients with indwelling urinary catheters and chronic bacteriuria showed no change in urinary pH (Nahata et al 1982), as did a double-blind study of 153 women (Avorn et al 1994). One small, open study involving 12 healthy subjects found that 330 mL of cranberry juice reduced the urinary pH (Kessler et al 2002).

OTHER ACTIONS
In vitro tests using four different *Vaccinium* spp. found that the proanthocyanidin fraction of cranberry exhibits potential anticarcinogenic activity (Bomser et al 1996). A non-specific antiviral effect has been demonstrated in vitro for a commercially produced cranberry fruit juice drink (Lipson et al 2007).

CLINICAL USE

Prevention of UTI
Controlled clinical trials support the use of cranberry products (solid-dose form and juice) in the prevention of UTI in women experiencing recurrent infections.

A 2008 systematic review evaluated data from 10 randomised controlled trials (RCTs) or quasi-RCTs of cranberry products for the prevention of

UTIs in all populations (n = 1049) (Jepson & Craig 2008). The effects of cranberry/cranberry-lingonberry juice versus placebo, juice or water were evaluated in seven studies, and cranberry tablets versus placebo in four studies (one study evaluated both juice and tablets). Overall, cranberry products significantly reduced the incidence of UTIs at 12 months compared with placebo/control. Cranberry products were more effective in women with recurrent UTIs than in the elderly or people requiring catheterisation. Only one study reported a significant result for the outcome of symptomatic UTIs. Side effects were common in all studies, and dropouts/withdrawals in several of the studies were high (Jepson & Craig 2008).

Previously, a 2004 Cochrane systematic review considered results from seven randomised clinical trials ultimately using data from two good-quality studies to undertake a meta-analysis (Jepson et al 2004, Kontiokari et al 2001, Stothers 2002). Once again, cranberry products were found to significantly reduce the incidence of UTI at 12 months compared with placebo/control in women, and there was no significant difference in the incidence of UTI between cranberry juice and cranberry capsules. One trial used 7.5 g of cranberry concentrate daily (in 50 mL), whereas the other trial used a 1:30 concentrate given either in 250 mL juice or in tablet form. Additionally, Stothers showed that cranberry tablets provided the most cost-effective prevention for UTI when compared with organic cranberry juice (Stothers 2002).

Spinal cord injuries

Patients with spinal cord injuries are a high-risk group for catheter-associated UTIs, so cranberry products are popular in this group. One double-blind, factorial design, randomised controlled trial of 305 people with spinal cord injuries showed no significant UTI-free period compared to placebo when taking 800 mg of cranberry tablets twice daily (Lee et al 2007), whilst another randomised, double-blind, placebo-controlled, crossover trial in 47 patients with spinal cord injury demonstrated a significant reduction in the frequency of UTIs (Hess et al 2008). An open, pilot study involving 15 volunteers with spinal cord injuries showed that three glasses of cranberry juice daily significantly reduced the adhesion of gram-negative and gram-positive bacteria to uroepithelial cells (Reid 2002). Treatment using catheter device with proanthocyanidin solutions has also been shown to inhibit adhesion of bacteria to non-biological particles such as PVC (Eydelnant & Tufenkji 2008).

Children

Cranberry use is popular for children with renal disease. An anonymous survey of 117 parents of children seen in a hospital paediatric nephrology clinic identified that 29% gave cranberry products to their children, to treat as well as prevent diverse renal problems (Super et al 2005). Most parents felt that it was beneficial and only one reported a side effect (nausea).

Two studies conducted with children managed by clean intermittent catheterisation found no clinical or statistical difference in the number of symptomatic UTI observed in either the cranberry or placebo groups (Foda et al 1995, Schlager et al 1999). Foda et al used a dose of 5 mL/kg/day of cranberry cocktail for 6 months and the dose used by Schlager was 2 ounces (≈55 g) of cranberry concentrate.

Treatment of UTI

Although cranberry may be a viable adjunctive treatment in UTI when antibiotic resistance is encountered, there is no reliable evidence that it is an effective sole treatment in diagnosed UTI (Ulbricht & Basch 2005). One study of pregnant women demonstrated comparable effects of daily cranberry juice cocktail to those of placebo for asymptomatic bacteriuria and symptomatic UTIs; however, the results were not statistically significant and more than one-third of participants withdrew from the study because of gastrointestinal upset (Wing et al 2008). In another study, cranberry exhibited only weak antimicrobial activity in urine specimens of symptom-free subjects after ingestion of a single dose (Lee et al 2008b).

Nephroprotection

Cranberries have an anti-inflammatory effect through their antioxidant function and might prevent infection-induced oxidative renal damage. Animal studies suggest that cranberries might be used clinically as a beneficial adjuvant treatment to prevent damage due to pyelonephritis in children with vesico-ureteric reflux (Han et al 2007).

Urinary deodorising activity

Cranberry juice and solid-dose forms are popular in nursing homes as urinary deodorising agents in older adults with incontinence. Although no clinical study is available to confirm efficacy, numerous anecdotal reports suggest that it is useful when used on a regular basis.

OTHER USES

Gout

Cranberry juice has been used to treat gout. Evidence of increased uric acid excretion in humans provides a theoretical basis for the indication, although studies in patients with gout are not available to confirm effectiveness (Kessler et al 2002).

Oral hygiene

The antiadhesion effect of cranberry on oral microbial flora has been demonstrated in vitro (Bodet et al 2008, Koo et al 2006, Yamanaka et al 2007). More specifically, cranberry polyphenol fraction significantly decreased the hydrophobicity of oral streptococci in a dose-dependent manner suggesting that it may reduce bacterial adherence to the tooth surface (Yamanaka-Okada et al 2008).

Prevention and treatment of *Helicobacter* infection

Cranberry inhibits the adhesion of *H. pylori* to human gastrointestinal cells in vitro (Matsushima et al 2008); however, very little clinical evidences are

available to confirm significance in humans (Burger et al 2002). A multicentric, randomised controlled, double-blind trial found that regular intake of cranberry juice or a probiotic inhibited *H. pylori* in a trial of 295 children (Gotteland et al 2008). Another double-blind, randomised clinical study was carried out in 177 patients with *H. pylori* infection to investigate possible additive effect of cranberry juice to triple therapy with omeprazole, amoxicillin and clarithromycin (OAC). Overall, there was no statistically significant difference; however, analysis by gender showed that the eradication rate was higher in females taking cranberry, but not in males (Shmuely et al 2007).

Chemoprotection

Studies employing mainly in vitro tumour models show that cranberry extracts and compounds inhibit the growth and proliferation of several types of tumour, including lymphoma, bladder, breast, colon, prostate, ovaries, oesophageal, lung and oral squamous cell carcinoma (Chatelain et al 2008, Ferguson et al 2006, Hochman et al 2008, Kresty et al 2008, Prasain et al 2008, Singh et al 2009, Sun & Hai Liu 2006). The flavonoid components may act in a complementary fashion to limit carcinogenesis by inducing apoptosis in tumour cells (Neto et al 2008).

Cardioprotection

Consumption of 250 mL cranberry juice daily is associated with decreasing markers of oxidative stress (Ruel et al 2008) and a significant increase in plasma HDL cholesterol concentration (Ruel et al 2006). In addition, cranberry extract increases cholesterol uptake and the synthesis of LDL receptors (Chu & Liu 2005), suggesting that accelerated cholesterol excretion may occur in vivo (McKay & Blumberg 2007).

Type 2 diabetes

Some studies have suggested that consumption of a low-calorie cranberry juice is associated with a favourable glycaemic response (Wilson et al 2008a, 2008b); however, a randomised, placebo-controlled, double-blind study demonstrated that cranberry had a neutral effect on glycaemic control in type 2 diabetics. This same study found, however, that cranberry supplements are effective in reducing atherosclerotic cholesterol profiles, including LDL cholesterol and total cholesterol levels, as well as total:HDL cholesterol ratio in people with type 2 diabetes (Lee et al 2008a).

DOSAGE RANGE

Preventing UTI

- According to clinical studies:
  Adults: 30–300 mL daily or 400 mg capsule daily.
  Children: 15 mL/kg or up to 300 mL daily.

In practice, much higher doses are being used in an attempt to achieve quicker results (e.g. cranberry capsules or tablets 10,000 mg/day for prevention).

ADVERSE REACTIONS

At high doses (3 L or greater), gastrointestinal discomfort and diarrhoea can occur (Ulbricht & Basch 2005).

SIGNIFICANT INTERACTIONS

Proton pump inhibitors

The composition of bioactive components of cranberry juice can vary substantially and there is potential for drug interaction (Ngo et al 2009).

Cranberry juice increases the absorption of vitamin B12 when used concurrently with PPI medicines (Saltzman et al 1994) — beneficial interaction.

Warfarin

There are a number of case reports suggesting that cranberry juice may increase the INR in patients taking warfarin; however, two case reports did not clearly identify cranberry juice as the sole cause of INR elevation, whereas one case report appeared to show a correlation between the effects of cranberry juice and warfarin metabolism (Pham & Pham 2007). In contrast, results from two clinical pharmacokinetic studies indicate no clinically relevant pharmacokinetic interaction between cranberry juice and warfarin (Pham & Pham 2007). One clinical study found that cranberry juice did not change the anticoagulant effect of warfarin and daily ingestion of cranberry juice did not inhibit the activities of CYP2C9, CYP1A2 or CYP3A4 (Lilja et al 2007). A more recent study suggests that a pharmacodynamic interaction is more likely (Mohammed Abdul et al 2008).

Until the interaction can be better understood, patients taking warfarin with cranberry juice should be cautioned about a potential interaction and monitored closely for INR changes and signs and symptoms of bleeding.

CONTRAINDICATIONS AND PRECAUTIONS

People with diabetes should take care when using commercially prepared cranberry juices because of the high sugar content.

If symptoms of UTI become more severe while cranberry is being administered, other treatments may be required and medical advice is recommended.

People with a history of oxalate kidney stones should limit their intake of cranberry juice.

PREGNANCY USE

Women experience UTIs with greater frequency during pregnancy. A systematic review of the literature for evidence on the use, safety and pharmacology of cranberry, focusing on issues pertaining to pregnancy and lactation found that there is no direct evidence of safety or harm to the mother or fetus as a result of consuming cranberry during pregnancy. Indirectly, there is good scientific evidence that cranberry may be of minimal risk, where a survey of 400 pregnant women did not uncover any adverse events when cranberry was regularly consumed. In lactation, the safety or harm of cranberry is unknown. Given the evidence to support the use of cranberry for urinary tract infections and its safety profile, cranberry supplementation as fruit or fruit juice is an appropriate and valuable therapeutic choice in the treatment of UTIs during pregnancy (Dugoua et al 2008).

PRACTICE POINTS/PATIENT COUNSELLING

- Cranberry preparations are widely used to prevent and treat minor UTI.
- Overall, clinical testing suggests that the juice and solid-dose forms may have significant beneficial effects for UTI management.
- Cranberry exerts bacteriostatic effects by reducing bacterial adhesion to host tissues.
- Overall, evidence suggests no significant alteration to urinary pH at doses less than 330 mL daily.
- Cranberry products have also been used to treat gout and to deodorise urine in people with incontinence.
- Preliminary research suggests a possible role in preventing conditions such as *Helicobacter pylori* infection and dental plaque formation.
- Patients taking warfarin and regular cranberry intake should have their INR monitored.

PATIENTS' FAQs

What will this herb do for me?

Cranberry products appear to reduce the risk of developing UTI.

When will it start to work?

Studies using 1–2 glasses of cranberry juice suggest that 4–8 weeks' continual use is required; however, faster effects using concentrated tablets or capsules have been reported.

Are there any safety issues?

If fever or pain exists or symptoms of UTI become more severe, seek medical advice. People taking warfarin together with cranberry should monitor their INR for changes.

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Creatine

HISTORICAL NOTE Creatine was first discovered in 1832 when it was identified in meat. The word creatine is derived from the Greek *kreas* for flesh, similar to the word 'creature'. About 15 years later, the meat from foxes killed in the wild were found to have 10-fold more creatine than meat from domesticated foxes, suggesting that physical exercise must influence the amount of creatine that accumulates in muscles. Early last century, orally consumed creatine was shown to be partly retained in the body and able to increase creatine content in muscles, leading some to suspect this could influence the performance of muscles. Nowadays, creatine monohydrate enjoys enormous popularity as a sports supplement and is being recommended to elite athletes by respected sporting bodies such as the Australian Institute of Sport (AIS 2009).

BACKGROUND AND RELEVANT PHARMACOKINETICS

Creatine is a naturally occurring nitrogenous compound produced in the human liver, pancreas and kidneys at a rate of 1–2 g daily. It is synthesised from the amino acids glycine, arginine and methionine and stored primarily in skeletal muscle, where it is in dynamic equilibrium with phosphocreatine and is a precursor to adenosine triphosphate (ATP), the main source of energy for muscle activity and many other biological functions. Orally ingested creatine is absorbed from the small intestine, then distributed via creatine transporters around the body to muscles and nerves (Persky et al 2003). These transporters also serve as a clearance mechanism because of creatine 'trapping' by skeletal muscle. It is ultimately converted to creatinine and excreted by the kidneys.

CHEMICAL COMPONENTS

Creatine is chemically known as *N*-(aminoiminomethyl)-*N*-methyl glycine.

FOOD SOURCES

Animal protein and fish. It has been estimated that approximately 1–2 g are ingested daily from the diet by non-vegetarians (Hendler 2001).

DEFICIENCY SIGNS AND SYMPTOMS

Several rare inborn errors of metabolism that result in a lack of creatine and phosphorylcreatine in the brain and severe mental retardation have been identified. Other symptoms and signs, such as involuntary extrapyramidal movements, speech disability, epilepsy, muscular hypotonia and weakness, and, in older patients, autism with

self-injurious behaviour have also been reported (Wyss & Schulze 2002).

People involved in intense physical activity, vegetarians and those with muscle diseases may have low creatine levels.

MAIN ACTIONS

Energy production

Although the exact mechanism is unknown, much is known about the biochemistry of endogenous creatine. In skeletal muscle tissue, it is used for the production of phosphocreatine, an important form of high-energy phosphate. Phosphocreatine is broken down into phosphate and creatine during high-intensity exercise lasting 15–30 s. During the process, energy is released and is used to regenerate ATP, the primary source of energy.

Supplemental creatine

Oral supplementation with creatine has been shown to increase phosphocreatine levels in muscles, and as such, has been described as 'fuelling up' natural energy stores. Increased creatine stores leads to faster regeneration of ATP, thereby making more energy immediately available to muscles. Theoretically, increased free creatine allows depleted stores to replenish more quickly, thus shortening recovery times during repeated bouts of intense exercise. Increased muscle creatine may also buffer the lactic acid produced during exercise, delaying muscle fatigue and soreness.

It has been estimated that short-term supplementation over 5–7 days with a daily dose of 20 g creatine increases total creatine content by 10–30% and phosphocreatine stores by 10–40% (Kreider 2003).

In clinical studies, the effect of creatine on performance, endurance, strength and recovery is variable.

Neuroprotective

Creatine supplementation has displayed neuroprotective effects in several animal models of neurological diseases, such as Huntington's disease, Parkinson's disease, or motor neuron disease (MND) (also known as amyotrophic lateral sclerosis) (Andreassen et al 2001, Dedeoglu et al 2003, Ferrante et al 2000, Wyss & Schulze 2002). The National Institute of Neurological Disorders and Stroke (NINDS) is currently conducting a large double-blind, placebo-controlled, phase III study involving 1720 people with early-stage Parkinson's disease to evaluate the effects of long-term creatine supplementation.

Creatine may exhibit antiageing benefits according to an in vivo study where creatine-fed mice lived longer and exhibited improvements in neurobehavioural tests. Further, creatine significantly lowered the amounts of ageing pigment, lipofuscin and upregulated various genes involved in neuroprotection and learning (Bender et al 2008). Preliminary data from a randomised, comparative, open study has shown a neuroprotective effect in cases of children with traumatic brain injury. Treatment with creatine improved a number of parameters, including duration of post-traumatic amnesia, length of recovery time, social/behaviour and cognitive function (Sakellaris et al 2006). A number of theories of a possible mechanism for neuroprotection have been put forward. One theory proposes that creatine exerts antioxidant activity and mitochondrial stabilising effects, two mechanisms of benefit in neurodegenerative diseases, which are characterised by mitochondrial dysfunction and oxidative damage (Shefner et al 2004). Recently, oral doses of creatine have been shown to pass the blood brain barrier (Andres et al 2008).

OTHER ACTIONS

A recent animal model demonstrated a 40% reduction in infarct volume after stroke. By using magnetic resonance imaging (MRI) the study found augmented cerebral blood flow after stroke in the mice treated with creatine (Prass et al 2006). Research in animal models has shown that it inhibits the growth of some solid tumours and also exhibits antioxidant activity (Lawler et al 2002). In a rat model, creatine monohydrate exhibited a positive influence on bone mineral density (Antolic et al 2007).

CLINICAL USE

Creatine monohydrate is the form generally used and tested. In practice, this is available in three different forms, which differ according to particle size (granular, powder and micronised), with the belief that smaller particles are more fully absorbed and cause less gastric distress.

Ergogenic aid

Creatine supplementation has become one of the most widely used supplements taken by athletes and is touted by some as the only truly effective ergogenic aid, besides carbohydrate loading. It is used by athletes engaged in sprint disciplines (e.g. 100 m run or 50 m swim), strength disciplines (e.g. weight lifting) or high-intensity, repetitive burst exercise (e.g. tennis, hockey, football, soccer) separated by short bouts of recovery. Its use is based on the assumption that supplementation at doses above dietary levels will increase energy and power output and also enhance recovery.

Hundreds of small studies have attempted to evaluate the effects of creatine supplementation on exercise capacity and muscle physiology in various populations.

A 2003 review of the literature concluded that approximately 300 studies have evaluated its potential as an ergogenic aid, with about 70% of studies reporting statistically significant positive results (Kreider 2003).

Who will respond?

The observation that not every athlete responds to creatine supplementation with improved strength, performance and recovery has prompted investigation to identify the key features of responders. One study identified that responders had the lowest initial levels of muscle creatine, greatest percentage of type 2 fibres, greatest preload muscle fibre

cross-sectional area and fat-free mass in comparison to non-responders (Syrotuik & Bell 2004). Other factors that are likely to influence an individual's response to creatine include training status, diet, age and the bioavailability of the creatine supplement being used. One review on the use of creatine in the elderly suggested that timing of creatine intake may be important, and if creatine is taken closely before or after the resistance training session it is likely to be more effective (Candow & Chilibeck 2008). Not taking these factors into account may partly explain the inconsistent results obtained in randomised studies.

Short duration, high-intensity exercise

Most, but not all, controlled studies have shown that supplementation improves performance and delays muscle fatigue (Balsom et al 1995, Becque et al 2000, Burke et al 1996, Cox et al 2002, Finn et al 2001, Gilliam et al 2000, Kreider et al 1998, Maganaris & Maughan 1998, Mujika & Padilla 1997, Mujika et al 2000, Tarnopolsky & MacLennan 2000, Williams & Branch 1998). One small study with 10 cyclists found improved sprint cycling in the heat with a dose of 5 g given four times a day for 6 days (Wright et al 2007). A recent trial with 18 players during an 8-week rugby season of Rugby Union football found that creatine, at a relatively low dose (0.1 g/kg/day) increased muscular endurance without detrimentally affecting body composition or aerobic endurance (Chilibeck et al 2007). Other trials, such as a placebo, RCT with 17 ice hockey players given 0.3 g/kg/day of creatine for 5 days (Cornish et al 2006), show no benefits. Also a recent double-blind study found no significant improvement on multiple sprint performance, fatigue or blood lactate concentration when testing creatine use with 42 physically active men who were given 5 g four times a day for 5 days (Glaister et al 2006). One recent study of 13 volunteers given creatine over 4 weeks found that creatine had no effect on metabolic adaptation in endurance training (Reardon et al 2006). In these recent studies, creatine monohydrate was used and the dosages were similar, but given that the studies were all small it may be that larger studies would produce more consistent findings. Another explanation for the differences in the results of these studies is that almost 30% of athletes are thought to be non-responders to creatine (possibly due to adequate creatine levels or a different make-up of their muscle fibres). It is possible that creatine use is beneficial in short-duration anaerobic exercise but not for endurance performance (Calfee & Fadale 2006).

Studies have been conducted in a variety of athletes, such as sprint cyclists, soccer players and sprint swimmers, and generally used a dose of 20 g daily. A recent study with tennis players found no significant benefits of creatine on repetitive sprint power or in muscular strength (Pluim et al 2006).

Lean body mass

Creatine increases exercise-related gains in lean body mass (Chrusch et al 2001, Jowko et al 2001, Stone et al 1999), although some of these apparent gains may actually represent water retention in the muscles.

Enhanced power

Many studies show that creatine supplementation in conjunction with resistance training augments muscle strength and size, although the effect is not consistent for everybody (Spriet & Gibala 2004, Volek & Rawson 2004). A 2003 review of 22 studies estimated that the average increase in muscle strength following creatine supplementation as an adjunct to resistance training was 8% greater than the placebo (20% vs 12%) (Rawson & Volek 2003). Similarly, the average increase in weightlifting performance (maximal repetitions at a given percentage of maximal strength) following creatine supplementation plus resistance training was 14% greater than the placebo (26% vs 12%).

Creatine supplementation increases muscle fibre hypertrophy, myosin heavy chain expression and swelling of myocytes, which may in turn affect carbohydrate and protein metabolism. Supplementation also increases acute weightlifting performance and training volume, which may allow for greater overload and adaptation to training. According to a double-blind, placebo study, creatine in combination with physical training increases fibre growth by increasing satellite cell number and myonuclei concentration. Researchers took muscle biopsies at various intervals during 16 weeks of heavy resistance training where participants were given 6 g of creatine monohydrate four times a day for the loading phase of 7 days and then once a day (Olsen et al 2006).

Some studies show no benefits of adding supplementation to a training protocol on either strength or lean body mass. In one study, creatine monohydrate was given at a dose of 0.3 g/kg for 7 days and then 0.03 g/kg for 9 weeks, and resistance training was carried out for 4 days a week. This study was of 26 females and it may be that the non-response was due to the gender (Ferguson & Syrotuik 2006). Another study of 42 elderly males found that creatine supplementation did not confer any extra benefits to isotonic exercise training and did not enhance muscle adaptability (Carter et al 2005). In this double-blind, randomised, placebo-controlled study, 7 g creatine per day were administered in the 1-week loading phase and then 5 g creatine a day for the remainder of the 16-week study, and the volunteers undertook resistance training for 3 days a week.

Reducing strength decline in the elderly

The effects of supplemental creatine in older adults have been investigated in a few studies, overall producing positive results (Brose et al 2003, Chrusch et al 2001, Kreider et al 1998). One randomised, double-blind study involving 30 older men (> 70 years) showed that resistance training combined with creatine supplementation produced significantly greater increases in lean tissue mass, leg strength, endurance and average power than placebo (Chrusch et al 2001). The dose regimen used was 0.3 g/kg for the first 5 days followed by 0.07 g/kg thereafter. Another double-blind study in 28 men and women aged

over 65 years showed that creatine supplementation (5 g daily) combined with resistance training enhanced the increase in total and fat-free mass, and gains in several indices of isometric muscle strength (Brose et al 2003). A recent double-blind, placebo, RCT with 14 days of creatine supplementation in elderly men and women confirmed significant increases in grip strength, muscle endurance and physical working capacity at fatigue threshold (Stout et al 2007). In contrast, a 7-day study of elderly women produced mixed results, as creatine supplementation (dosage 0.3 g/kg/day) did not show any benefits for endurance but did help volunteers to perform lower body function exercises that involved quick movements (Canete et al 2006).

Cervical level spinal cord injury

According to a randomised, double-blind, placebo-controlled crossover trial, creatine supplementation enhances upper extremity work capacity in subjects with complete cervical level spinal cord injury (Jacobs et al 2002).

Bone mineral density

According to a double-blind, placebo-controlled study with 29 older men, creatine (0.3 g/kg for 5 days and 0.07 g/kg thereafter) administered for 12 weeks while undergoing resistance training significantly increased bone density. Creatine supplementation had an additional benefit for regionalised bone mineral content where there was a change in lean tissue mass. It was suggested that the effect may be due to greater tension on the bone due to an increase in muscle mass in the creatine participants (Chilibeck et al 2005).

Muscular dystrophy

A number of muscle diseases are associated with a decrease in intracellular creatine concentration, which could theoretically contribute to muscle weakness and degeneration of muscle tissue (Wyss et al 1998).

One double-blind, crossover study of 36 patients with various muscle diseases found that creatine supplementation over 8 weeks produced a mild but significant improvement in muscle strength and daily-life activities on Medical Research Council scales and the Neuromuscular Symptom Score (Walter et al 2000). A single-blind, placebo-controlled trial of 21 volunteers with different neuromuscular disorders found that creatine supplementation (10 g daily for 5 days followed by 5 g daily for 5–7 days) produced significant improvements in body weight, handgrip, dorsiflexion and knee extensor strength (Tarnopolsky et al 1997). A recent review concluded that creatine has therapeutic potential in Duchenne muscular dystrophy due to its ability to increase fat-free mass and muscle strength. Further long-term studies were recommended to assess benefits and any side effects (Pearlman & Fielding 2006).

A recent systematic review of literature looking at creatine supplementation in muscle diseases evaluated 12 randomised trials and found the evidence demonstrated that both short- and medium-term creatine supplementation improved muscular strength in those with muscular dystrophies but no significant improvement in metabolic myopathies. However, people with glycogen storage disease type V should avoid high-dose creatine supplementation, as it caused a significant increase in pain in one study (Kley et al 2007).

Clinical note — The Australian Institute of Sport Supplement Program

The AIS is world renowned for its professionalism and high-quality training programs. In 2000, a project called the AIS Sports Supplement Program (AIS 2009) was developed to ensure that athletes use supplements correctly and confidently, and receive 'cutting edge' advice on nutritional practices. In order to streamline the information available, a panel of experts categorised some of the most popular sports supplements into various classes to clarify which are approved or recommended and which are directly banned by international doping rules. Some of the approved supplements recommended for use include creatine, antioxidants (vitamins C and E), multivitamins, iron, calcium supplements and sports drinks.

Congestive heart failure

Muscle fatigue due to loss of skeletal muscle mass and strength, decreased oxidative capacity and other abnormalities of muscle metabolism have been associated with congestive heart failure. As a result, creatine supplementation has been suggested as a possible therapeutic agent in this condition.

A dose of 10 g creatine daily for 7 days significantly increased exercise capacity and muscle strength compared to placebo in a double-blind study involving 17 men with congestive heart failure (Gordon et al 1995). However, creatine supplementation did not alter ejection fraction at rest or at work. Muscle endurance during handgrip exercises was also seen to improve in another double-blind, crossover study of 20 men given 5 g creatine four times daily for 5 days (Andrews et al 1998). Another study using the same dose of creatine, for 6 weeks, in a double-blind, placebo, crossover study with 20 congestive heart failure patients found an increase in body weight and muscular strength which occurred only during the supplementation period and not beyond. There was no significant change in peak oxygen uptake, walking distance or quality of life (Kuethe et al 2006).

Neurological degenerative diseases

Over the past few years, a considerable body of scientific evidence has given support to the idea that creatine supplementation may alleviate some of the clinical symptoms of neurological disease and delay disease progression (Wyss & Schulze 2002). Unfortunately, neuroprotective effects demonstrated in animal models have not been consistently demonstrated in clinical trials. This may be not only because the pathophysiological processes of

neurodegenerative disease are different in humans, but also due to differences in dosage and timing of creatine supplementation. Some animal studies have used doses 10 times higher than in clinical trials. Clearly, further investigation is warranted (Andres et al 2008).

Huntington's disease

A number of studies conducted with experimental animal models of Huntington's disease have identified a possible role for creatine supplementation (Andreassen et al 2001, Dedeoglu et al 2003, Ferrante et al 2000). Creatine was shown to increase survival, delay onset of symptoms and exert neuroprotective effects in vivo. A recent double-blind, placebo RCT with 64 Huntington's disease patients given creatine at a dose of 8 g/day for 16 weeks found that creatine concentrations in the brain and serum increased with supplementation and reduced oxidative injury to DNA (Hersch et al 2006).

Parkinson's disease

Decreased muscle mass and strength is a feature of Parkinson's disease. Creatine monohydrate combined with resistance training showed improved muscular endurance and improvements in upper body strength. This double-blind, placebo, RCT had 20 patients given 20 g/day of creatine for 5 days and then 5 g/day for 12 weeks (Hass et al 2007). Another recent placebo, RCT followed 60 patients for a 2-year period and found that creatine had no overall effect on Unified Parkinson's Disease Rating Scale scores (which covers behaviour and mood, daily living activities, motor skills and complications of therapy; patients taking creatine did experience elevated mood and required smaller increases in dopamine medication) (Bender et al 2006).

Motor neuron disease

A preliminary study demonstrated that creatine supplementation of 20 g daily for 7 days followed by 3 g daily for 3 and 6 months produced temporary increases in maximal isometric power in patients with MND (Mazzini et al 2001). Two randomised, double-blind, placebo-controlled studies have been conducted with MND patients, with both finding no change to disease progression with creatine monohydrate supplementation at doses of 5–10 g daily (Groeneveld et al 2003, Shefner et al 2004). Study periods varied from 6 to 12 months. The study by Shefner et al used creatine monohydrate at a loading dose of 20 g/day for 5 days, followed by 5 g/day. It must be noted that this study was powered only to detect a 50% or greater change, so the failure to show a significant positive effect of treatment might have limited clinical significance.

Charcot-Marie-Tooth Disease (CMT)

Muscle function improved when creatine and resistance training was undertaken by people with CMT according to a randomised, placebo-controlled trial of 18 people. Over the 12-week period, combined treatment also resulted in improved muscle myosin heavy chain composition (Smith et al 2006).

Reduces mental fatigue and improves cognitive function

Creatine supplement (8 g/day for 5 days) reduced mental fatigue when examined under double-blind, placebo-controlled conditions in 24 healthy volunteers (Watanabe et al 2002).

An RCT found that creatine significantly improved tasks requiring speed of processing both working memory and intelligence (Raven's Advanced Progressive Matrices). This trial involved 45 healthy young vegetarians who are more likely to have lower creatine levels than non-vegetarians and possibly be more responsive to treatment (Rae et al 2003). A placebo, RCT demonstrated that creatine improved cognitive function in elderly patients with various cognitive performance tasks showing significant improvement on baseline, apart from backward number recall where no improvement was found (McMorris et al 2007). Alternatively, a negative double-blind, placebo-controlled study of 22 individuals given 0.03 g/kg of body weight of creatine per day for 6 weeks found no significant difference in cognitive function (Rawson et al 2008).

OTHER USES

Gyrate atrophy

Doses of 1.5 g/day for 1 year resulted in improvement of the skeletal muscle abnormality that accompanies gyrate atrophy, a genetically acquired form of blindness (Feldman 1999).

Diabetes

Creatine supplementation (10 g/day) for 3 months improved glucose tolerance but not insulin sensitivity when combined with aerobic training in a double-blind, randomised, placebo-controlled trial with 22 healthy sedentary males who consumed 10 g of creatine a day over 3 months (Gualano et al 2008).

DOSAGE RANGE

There are two common dosing regimens.

Loading

Creatine loading protocols have been well studied.

- *Rapid loading:* a dose of 5 g is taken four times daily for 5–7 days as a loading phase, followed by 2–10 g daily as maintenance for 1 week–6 months (Bemben & Lamont 2005). This is followed by a 4-week break and then restarted in a process known as 'cycling'.
- *Slower loading:* a similar effect can be achieved by taking 3 g daily over 28 days.

Concurrent ingestion of carbohydrate (50–100 g) may improve creatine uptake.

Once muscles have become saturated, it takes approximately 4 weeks to return to baseline levels.

Clinical note — Interview with Steve Brown, former Mr Australia and personal trainer

In practice, micronised forms of creatine monohydrate provide superior results to powders or granules and have less gastrointestinal side effects, particularly when taken with glucose or dark grape juice, according to Steve Brown (pers. commun. 2003). The loading regimen typically increases the ability to lift heavier weights for greater repetitions within 2–4 weeks and occurs quite suddenly. Also, creatine increases alertness and mental sharpness, effects that are obvious after the first week. Although there is a slight weight gain due to water retention, lean body mass also increases, because the body is able to work harder and for longer with creatine. Once supplementation stops, the physical effects on performance quickly reduce and are noticeable after the first week.

Non-loading

• Daily dose of 3 g.

In practice, creatine is often taken with simple carbohydrates, such as glucose or fruit juice, in order to increase creatine accumulation within muscle.

ADVERSE REACTIONS

Side effects include gastrointestinal distress with nausea and vomiting, diarrhoea, muscle fatigue, pain and cramping, dehydration and heat intolerance. The effects may be reduced when micronised forms of creatine are taken together with glucose or simple carbohydrates. Gastrointestinal disturbance may further be reduced if doses are divided (e.g. two doses of 5 g a day may be better tolerated than a single 10-g dose) (Ostojic & Ahmetovic 2008).

Fluid retention is commonly observed during the loading phase of supplementation and it can result in early weight gain of 1.6–2.4 kg.

SIGNIFICANT INTERACTIONS

Controlled studies are not available and there is insufficient reliable evidence to determine interaction potential.

CONTRAINDICATIONS AND PRECAUTIONS

Use of high-dose creatine is contraindicated in individuals with renal failure.

Caution in people with bipolar depression — two case reports suggest that creatine monohydrate supplementation may cause a manic episode (Roitman et al 2007).

A risk assessment report using data from clinical trials concluded that, overall, creatine has a good safety profile in healthy individuals with the main side effect being gastrointestinal upset when taken in large doses. Doses up to 5 g/day are generally considered safe but the long-term safety of larger doses is yet to be established (Shao & Hathcock 2006). Creatine supplementation for up to 8 weeks has not been associated with major health risks, but the safety of more prolonged creatine supplementation has not been established (Williams & Branch 1998).

PRACTICE POINTS/PATIENT COUNSELLING

- Creatine is a very popular sports supplement and is not a substance banned by the International Olympic Committee. Although scientific evidence supports its use in high-intensity, repetitive burst exercise, not every individual will respond. Investigation is underway to determine the key characteristics of athletes most likely to respond.
- Creatine is also used in the treatment of numerous conditions involving fatigue or muscle weakness, but little evidence is available yet to determine its effectiveness.
- Creatine is used in the production of ATP, the main source of energy for muscle activity and many other biological functions.
- Clinical studies suggest that creatine supplementation may improve cognitive function and mood.
  - Neuroprotective effects observed in animal studies and some clinical studies suggest a possible role in neurodegenerative diseases; however, further research is still required to clarify its role.
- In practice, creatine is often taken in high doses for 5–7 days, followed by lower maintenance doses for up to 8 weeks. This is called 'loading'.
- High-dose creatine is contraindicated in renal failure.

PREGNANCY USE

Insufficient reliable data are available, but it is generally not recommended in pregnancy.

PATIENTS' FAQs

What will this supplement do for me?

Creatine enhances physical power and recovery in most cases. It may also reduce mental fatigue, enhance mood and memory and have a protective effect on nerves. Research shows a possible role in neurodegenerative diseases, which remains to be confirmed.

When will it start to work?

The physical effects generally develop within 1–4 weeks of use.

Are there any safety issues?

It should not be taken in high doses by people with kidney disease and its long-term safety has not been established.

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Damiana

HISTORICAL NOTE Damiana is a wild deciduous shrub found in the arid and semi-arid regions of South America, Mexico, United States and West Indies. It is believed that Mayan Indians used damiana to prevent giddiness, falling and loss of balance, and as an aphrodisiac. It has also been used during childbirth, and to treat colic, stop bedwetting and bring on suppressed menses. Today its leaves are used for flavouring in food and beverages, and infusions and other preparations are used for a variety of medicinal purposes.

COMMON NAME
Damiana

OTHER NAMES
Herba de la pastora, Mexican damiana, miziboc, old woman's broom, shepherd's herb, stag's herb

BOTANICAL NAME/FAMILY
Turnera diffusa, Damiana aphrodisiaca, Turnera aphrodisiaca (family Turneraceae)

PLANT PARTS USED
Dried leaves and stems

CHEMICAL COMPONENTS
Sesquiterpenes, alkaloids, essential oils containing caryophyllene, delta-cadinene, beta-elemene and 1,8-cineol and other lesser constituents, tetraphylin B (a cyanogenic glycoside, 0.26%), resin, tannins, gum, mucilage, starch, a bitter element and possibly caffeine. Damiana also contains a flavone and at least five flavonoids, including arbutin (Piacente et al 2002).

MAIN ACTIONS
The pharmacological actions of damiana have not been significantly investigated, so traditional use and in vitro and in vivo evidence is used.

Hormonal effects
One study that investigated the effects of over 150 herbs for their relative capacity to compete with oestradiol and progesterone binding to intracellular receptors identified damiana as a herb that binds to intracellular progesterone receptors, exerting a neutral effect and also exerting weak oestrogen agonist activity (Zava et al 1998). It has been reported that delta-cadinene is a testosterone inducer and 1,8-cineole is a testosterone hydroxylase inducer (Duke 2006). A study analysing the constituents of the essential oils found in various damiana samples identified that fresh and dry samples contained both compounds, but wild plants contained more delta-cadinene than cultivated plants (Alcaraz-Melendez et al 2004). The action of these constituents may support the common belief that damiana is useful as an aphrodisiac.

Anti-inflammatory activity
A significant anti-inflammatory activity was identified for the aqueous and ethanolic fractions of damiana in an experimental model (Antonio & Souza Brito 1998). Antiplatelet activity was not observed.

Hypoglycaemic agent
A decoction of dried damiana leaves caused a significant reduction of the hyperglycaemic peak, exerting a hypoglycaemic effect comparable to that of tolbutamide in an experimental model (Alarcon-Aguilara et al 1998).

CLINICAL USE
Damiana has not been significantly investigated under clinical trial conditions; therefore, evidence is derived from traditional use, in vitro and animal studies, and its clinical significance is unknown.

Sexual dysfunction or decreased libido

Damiana has been used traditionally for sexual dysfunction or as an aphrodisiac to enhance sexual activity. Scientific studies in experimental models provide preliminary support for its use in these conditions, but controlled trials are lacking. One in vivo study established that damiana fluid extract significantly improves the copulatory performance of sexually sluggish animals, but has no effect on normally functioning ones (Arletti et al 1999). The effect appears to be dose-dependent, as positive results were obtained only when the highest dose (1 mL/kg) was administered.

One clinical study of unknown design compared a herbal combination product consisting of ginseng, Ginkgo, damiana, L-arginine and a variety of vitamins and minerals with placebo in 77 female volunteers. After 4 weeks, 73.5% of the women in the treatment group reported an increase in sexual satisfaction compared with 37.2% receiving placebo (Ito et al 2001). Although promising, the role of damiana in achieving this result is unknown.

Diabetes

Although in vivo studies suggest significant hypoglycaemic activity, no clinical studies are available to determine whether the effects are clinically significant.

Weight loss

No controlled studies are available to determine the effectiveness of damiana as a stand-alone treatment in weight loss; however, one study that used a combination of herbs that included damiana has produced positive results. The randomised, double-blind study involving 47 overweight subjects tested a herbal combination product known as 'YGD' (*Yerbe mate*, *Paullinia cupana* and damiana) for weight loss activity. Treatment resulted in a prolonged gastric emptying time and a body weight reduction of 5.1 $\pm$ 0.5 kg compared with 0.3 $\pm$ 0.08 kg after placebo over 45 days. A 12-month follow-up revealed that weight loss was maintained in the active treatment group (Andersen & Fogh 2001). Until studies using damiana as sole therapy are conducted, the effectiveness of this herb in weight loss is still unknown.

OTHER USES

In practice, damiana is sometimes used to treat anxiety and depression associated with hormonal changes (e.g. menopause) or where there is a sexual factor involved. It is also used as a mild stimulant and aphrodisiac, to enhance stamina generally, and for nervous dyspepsia and constipation.

DOSAGE RANGE

- Dried leaf: 2–4 g taken three times daily.
- Infusion: pour a cup of boiling water onto one teaspoonful of the dried leaves and let infuse for 10–15 min. Drink three cups daily.
- Liquid extract (1:2) or solid dose equivalent: 20–40 mL/wk or 3–6 mL/day.

ADVERSE REACTIONS

There is insufficient reliable information available.

SIGNIFICANT INTERACTIONS

Controlled studies are not available; therefore, interactions are based on evidence of activity and are largely theoretical and speculative.

Hypoglycaemic agents

Additive effects are theoretically possible, with unknown clinical significance — observe patients.

CONTRAINDICATIONS AND PRECAUTIONS

Traditionally, the herb is not recommended for people with overactive sympathetic nervous system activity.

PREGNANCY USE

Safety in pregnancy has not been scientifically evaluated; however, no increase in fetal abnormalities has been observed from limited use in women (Mills & Bone 2005).

PRACTICE POINTS/PATIENT COUNSELLING

- Damiana is a herb with a traditional reputation as being an aphrodisiac, stimulant, mood enhancer and general tonic.
- Currently, evidence to support its use as an aphrodisiac is limited to research in animals, which has produced some positive results.
- In vivo studies have identified significant anti-inflammatory and hypoglycaemic activity, although human studies are still required to determine clinical significance.
- It is also suspected that the herb exerts some degree of hormonal activity.

PATIENTS' FAQs

What will this herb do for me?

Damiana has not been significantly tested in human studies, so much information is taken from traditional sources or preliminary research in animals. According to these sources, it may increase sexual function and libido in some cases of dysfunction, lower blood glucose levels and exert anti-inflammatory actions.

When will it start to work?

There is insufficient evidence to predict when effects may develop.

Are there any safety issues?

A long history of use suggests it is generally safe. However, scientific testing has not been conducted.

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Dandelion

HISTORICAL NOTE Dandelion grows as a perennial native herb throughout the Northern Hemisphere and as a weed in other temperate zones. It has a long history of medicinal and culinary use. Dandelion leaves are added to salads, providing a good source of minerals, and the roasted root is used as a coffee substitute. Dandelion leaves are traditionally used as a diuretic, and the root as a liver tonic.

OTHER NAMES

Blowball, cankerwort, common dandelion, lion's tooth, priest's crown, puffball, swine snout, taraxacum, wild endive, white endive

BOTANICAL NAME/FAMILY

Taraxacum officinale; synonyms: *Leontodon taraxacum*, *Taraxacum vulgare* (family Compositae [Asteraceae])

PLANT PARTS USED

Leaf and root

CHEMICAL COMPONENTS

Dandelion leaf and root contain slightly different constituents.

Overall, dandelion is a rich source of minerals, particularly potassium (Hook et al 1993), as well as iron, magnesium, zinc, potassium, manganese, copper, choline, selenium, calcium, boron and silicon (Queralt et al 2005), and a rich source of vitamins A, C, D and B complex (US Department of Agriculture 2003). The relatively high protein, fibre and linoleic acid content of dandelion leaves has led to suggestions that dandelion is a nutritious and underutilised food source (Escudero et al 2003). Dandelion's constituents also include triterpenes, flavonoid glycosides and various phenolic acids, as well as phytosterols, sugars and mucilage (Blumenthal et al 2000). The phenolic acids and flavonoids include chicoric acid (dicaffeoyltartaric acid) and quercetin glycosides, respectively (Schutz et al 2005).

MAIN ACTIONS

Diuretic

Dandelion leaf has been found to have a greater diuretic effect than the roots, with activity comparable to that of frusemide, without causing potassium loss because of the leaves' high potassium content (Newell et al 1996). A study using an infusion of dandelion root found that dandelion did not significantly increase diuresis in rats (Grases et al 1994), and no secondary metabolites showing major diuretic activity were found (Hook et al 1993).

Choleretic

The bitter constituents in dandelion root are believed to be responsible for increasing bile production and flow, as well as contributing to the root's mild laxative effects.

Hepatic enzyme induction

In vivo studies have demonstrated decreased activity of CYP1A2 and CYP2E enzymes and dramatic increases in levels of the phase II detoxifying enzyme UDP-glucuronosyl transferase in liver microsomes of rats receiving dandelion tea (Maliakal & Wanwimolruk 2001). The same study found that dandelion tea had no effect on the activities of CYP2D and CYP3A.

Anti-inflammatory and antioxidant activity

Pharmacological tests demonstrate that ethanol extract of dandelion (part used not reported) has anti-angiogenic, anti-inflammatory and antinociceptive actions through its inhibition of nitric oxide production and COX-2 expression and/or its antioxidative activity. Dandelion extract was shown to exhibit a mild analgesic and anti-inflammatory effect in mice (Tito et al 1993), and an aqueous dandelion extract was found to prevent diabetic complications due to lipid peroxidation and free radicals in diabetic rats (Cho et al 2002). Dandelion extract has also been found to have a protective effect against induced acute pancreatitis in rats (Seo et al 2005) and dandelion flower extract demonstrated marked antioxidant activity that has been attributed to its phenolic content, with suppression of reactive oxygen species and nitric oxide (Hu & Kitts 2003, 2005, Kery et al 2004). Extracts of dandelion flowers, roots and stem have been found to have significant OH-radical scavenging activity (Kaurinovic et al 2003).

OTHER ACTIONS

Traditionally, dandelion root is understood to have laxative activity and to stimulate digestion, whereas dandelion leaf has antirheumatic effects. Dandelion root infusion, which contains oligofructans,

has been found to stimulate the growth of multiple strains of bifidobacteria, suggesting its use as a probiotic (Trojanova et al 2004).

Dandelion may have antidiabetic actions because ethanolic extracts of whole dandelion exhibited insulin secretagogue activity (Hussain et al 2004) and dandelion in conjunction with various other herbal extracts has been shown to have an antihyperglycaemic effect in mice (Petlevski et al 2003). Plants of the genus Taraxacum (dandelions) have a history of use in Chinese, Arabian and Native American traditional medicine, to treat a variety of diseases, including cancer. An extract of dandelion leaf (but not root or flowers) has been demonstrated to decrease the growth of MCF-7/AZ breast cancer cells in vitro suggesting that it may be of value as an anticancer agent. There is preliminary scientific evidence from animal and in vitro studies that suggest the roots of *Taraxacum japonicum* (Japanese dandelion) may have a cancer preventative effect. The extract has been shown to induce cytotoxicity through TNF-alpha and IL-1-alpha secretion in vitro.

CLINICAL USE

The therapeutic effectiveness of dandelion has not been significantly investigated under clinical trial conditions, so evidence is derived from traditional, in vitro and animal studies.

Diuretic

Dandelion has a long history of use as a diuretic in well-established systems of traditional medicines; however, the scientific and clinical evidence to support this use is limited to animal studies (see above). The high potassium content of dandelion is considered to be partly responsible for any diuretic activity (Hook et al 1993).

A double-blind, randomised study of 57 women with recurrent cystitis found that a commercial preparation known as Uva-E (a combination of bearberry leaves and dandelion root) significantly reduced the frequency of recurrence of cystitis compared with placebo. At the end of 12 months, none of the patients taking Uva-E had a recurrence of cystitis, compared with 23% recurrence in the control group ($P < 0.05$) (Larsson et al 1993). The role of dandelion in achieving this result is unknown; however, the researchers suggested that its diuretic effect was likely to have contributed to the positive results.

Liver tonic

Dandelion has a long history of use as a liver tonic (Macia et al 2005); however, the scientific and clinical evidence to support this use is limited. Preliminary studies suggest that dandelion root stimulates the flow of bile.

Commission E approves the use of dandelion root and herb for disturbances in bile flow, loss of appetite and dyspepsia (Blumenthal et al 2000).

European Scientific Co-Operative on Phytotherapy (ESCOP 2003) recommends dandelion root for 'restoration of hepatic and biliary function, dyspepsia, and loss of appetite'.

OTHER USES

Dandelion has been used traditionally as a source of minerals and for treating diabetes, rheumatic conditions, heartburn, bruises and for recurrent hives, urticaria and eczema. It has also been used to treat various digestive complaints such as dyspepsia, lack of appetite and constipation (Newell et al 1996), as well as for breast and uterine cancers (Koo et al 2004). The sap has been used topically on warts (Guarrera 2005).

DOSAGE RANGE

Leaf

- Infusion of dried herb: 4–10 g three times daily.
- Fluid extract (25%): 4–10 mL three times daily.
- Fresh juice: 10–20 mL three times daily.

Root

- Decoction of dried root: 2–8 g three times daily.
- Tincture (1:5): 5–10 mL three times daily.
- Fluid extract (30%): 2–8 mL three times daily.
- Juice of fresh root: 4–8 mL three times daily.

ADVERSE REACTIONS

Dandelion is generally considered safe when consumed in amounts commonly found in foods. Side effects are rare, and the likelihood of dandelion leaf preparations causing a contact allergy is low. However, cross-reactivity may exist between dandelion and other members of the Compositae (Asteraceae) family, such as ragweed, mugwort, sunflower, daisy and chamomile (Cohen et al 1979, Fernandez et al 1993, Jovanovic et al 2004). The most common type of allergy to dandelion is dermatitis following direct skin contact. Contact allergy to herbal teas derived from the plant family was investigated in patients allergic to sesquiterpene lactones (SLs). Ninety percent had positive test reactions to the Compositae teas, mainly to those based on dandelion, German chamomile and wormwood. Children with a family or personal history of atopy, summer-related or -exacerbated dermatitis of any kind, may be more sensitive to exposure to Compositae weeds, especially dandelions.

Avoid in patients with hypersensitivity/allergy to dandelion or other member of the Asteraceae family.

SIGNIFICANT INTERACTIONS

Controlled studies are not available; therefore, interactions are based on evidence of activity and are largely theoretical and speculative.

Diuretic agents

Dandelion leaf may theoretically interact with other diuretics, although the clinical significance of this is unknown — observe patient.

Quinolone antibiotics

The high mineral content of dandelion may result in the formation of chelate complexes with quinolone antibiotics and reduce their absorption and bioavailability. This has been demonstrated in rats with *Taraxacum mongolicum* (Chinese dandelion) (Zhu et al 1999). While the clinical significance of

this is unknown, it is recommended to avoid concomitant use of these substances or to separate their dosing.

CONTRAINDICATIONS AND PRECAUTIONS

It is recommended that dandelion not be used by people with obstruction of the bile ducts or other serious diseases of the gall bladder (Blumenthal et al 2000).

PREGNANCY USE

Based on a long history of use in traditional medicine, dandelion is generally considered safe in pregnancy and lactation (Blumenthal et al 2000, McGuffin et al 1997).

PRACTICE POINTS/PATIENT COUNSELLING

- Dandelion leaf and root have a long tradition of culinary and medicinal use.
- Dandelion has been traditionally used as a diuretic and liver tonic. It has also been used to treat various digestive complaints such as dyspepsia, lack of appetite and constipation.
- The therapeutic effectiveness of dandelion has not been significantly investigated under clinical trial conditions, so evidence is derived from traditional, in vitro and animal studies.
- Dandelion is generally considered to be safe and non-toxic, but may cause allergy in people allergic to ragweed and daisies.

PATIENTS' FAQs

What will this do for me?

In practice, dandelion is used to improve digestion and detoxification, as a diuretic and laxative and to treat diabetes, rheumatic conditions, heartburn, bruises and for recurrent hives, urticaria and eczema. Controlled studies are not available to determine its effectiveness in these conditions.

When will it work?

Stimulation of digestive processes is thought to occur rapidly after one dose.

Are there any safety issues?

Dandelion is generally considered to be safe and non-toxic but may cause allergy in people allergic to ragweed and daisies.

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Devil's claw

HISTORICAL NOTE The botanical name *Harpagophytum* means 'hook plant' in Greek, after the hook-covered fruits of the plant. Devil's claw is native to southern Africa and has been used traditionally as a bitter tonic for digestive disturbances, febrile illnesses and allergic reactions, and to relieve pain (Mills & Bone 2000). It has been used in Europe for the treatment of rheumatic conditions for over 50 years, and was first cited in the literature by Zorn at the University of Jena, Germany, who described his observations on the antiphlogistic and anti-arthritic effects after administration of oral aqueous extracts prepared from the secondary roots of *H. procumbens* in patients suffering from arthritides (Chrubasik et al 2006).

COMMON NAMES
Devil's claw root, grapple plant, harpagophytum, wood spider

BOTANICAL NAME/FAMILY
Harpagophytum procumbens (family Pedaliaceae)

PLANT PART USED
Dried tuber/roots

CHEMICAL COMPONENTS
The major active constituent is considered to be the bitter iridoid glucoside, harpagoside, which should constitute not less than 1.2% of the dried herb. Other iridoid glycosides include harpagide, procumbide, 8-O-(p-coumaroyl)-harpagide and verbascoside. About 50% of the herb consists of sugars. There are also triterpenes, phytosterols, plant phenolic acids, flavonol glycosides and phenolic glycosides. *Harpagophytum zeyheri*, which has a lower level of active compounds, may be partially substituted for *H. procumbens* in some commercial preparations (Stewart & Cole 2005). The extraction solvent (e.g. water, ethanol) has a major impact on the active principle of the products (Chrubasik 2004a). When administering *H. procumbens* extract topically it was found that higher penetration of all compounds occurred from an ethanol/water preparation (Abdelouahab & Heard 2008b).

MAIN ACTIONS

Anti-inflammatory/analgesic
There is good in vitro and in vivo pharmacological evidence of the anti-inflammatory and analgesic properties of devil's claw, although some negative findings have also been reported (McGregor et al 2005). Overall, greatest activity appears to be in semi-chronic rather than acute conditions.

Devil's claw exerted significant analgesic effects against thermally and chemically induced nociceptive pain stimuli in mice and significant dose-related reduction of experimentally induced acute inflammation in rats (Mahomed & Ojewole 2004), as well as reducing pain and inflammation in Freund's adjuvant-induced arthritis in rats (Andersen et al 2004). Results from a recent study in mice suggest that the opioid system is involved in the antinociceptive effects of *H. procumbens* extract (Uchida et al 2008).

The iridoids, particularly harpagoside, are thought to be the main active constituents responsible for the anti-inflammatory activity, although the mechanism of action is unknown and devil's claw is also rich in water-soluble antioxidants (Betancor-Fernandez et al 2003). More recent in vitro evidence suggests that the anti-inflammatory effect may in part be due to antioxidant activity (Denner 2007, Grant et al 2009, Langmead et al 2002). A study administering *H. procumbens* extract intraperitoneally to rats found that the anti-inflammatory response does not depend on the release of adrenal corticosteroids (Catelan et al 2006).

Contradictory evidence exists as to whether devil's claw affects prostaglandin (PG) synthesis. Early in vitro and in vivo studies suggest that it does not inhibit PG synthesis (Whitehouse et al 1983) and this is supported by studies of PG production in humans (Moussard et al 1992). However, more recent investigations have suggested that its anti-inflammatory and analgesic activities are due to suppression of PGE_2 synthesis and nitric oxide production and that the herb may suppress expressions of COX-2 and iNOS (Jang et al 2003). Harpagoside alone has been shown to suppress COX-2 and iNOS at both the mRNA and protein level in vitro due to a suppression of NF-kappaB activation (Huang et al 2006). Recent in vitro research shows that harpagoside and 8-O-(p-coumaroyl)-harpagide exhibit a greater reduction in COX-2 expression than verbascoside and that harpagide on the other hand causes a significant increase in COX-2 expression (Abdelouahab & Heard 2008a). Additionally, methanolic extracts of devil's claw have been shown to inhibit COX-2 in vivo (Kundu et al 2005, Na et al 2004).

Inhibition of leukotriene synthesis has been observed in vitro, which appears to relate to the amount of harpagoside present (Loew et al 2001). A study using subcritical and supercritical CO_2 extracts (15 to 30% harpagoside) showed almost total inhibition of 5-lipoxygenase biosynthesis at 51.8 mg/mL of extract, whereas the conventional extract (2.3% harpagoside) did not inhibit the enzyme significantly (Gunther et al 2006).

In vivo experiments have determined that the method of administration of devil's claw affects its anti-inflammatory properties. Intraperitoneal and intraduodenal administration was shown to reduce carrageenan-induced oedema, whereas oral administration had no effect, suggesting that exposure to stomach acid may reduce its anti-inflammatory activity (Soulimani et al 1994). This is supported by a study that found a loss of anti-inflammatory activity after acid treatment (Bone & Walker 1997).

In vitro studies on rat mesangial cells suggest that devil's claw may be used as an anti-inflammatory agent in the treatment of glomerular inflammatory diseases (Kaszkin et al 2004a). Devil's claw extract produced a concentration-dependent suppression of nitrite formation in rat mesangial cells in vitro due to an inhibition of iNOS expression through interference with the transcriptional activation of iNOS. It was found that this activity was due to harpagoside, together with other constituents that possibly have strong anti-oxidant activity (Kaszkin et al 2004b).

It has been suggested that the suppression of inflammatory cytokine synthesis, demonstrated in vitro and vivo (Fiebich et al 2001, Spelman et al 2006), could explain its therapeutic effect in arthritic inflammation (Kundu et al 2005). Fiebich and co-workers found that a 60% ethanolic extract decreases the expression of IL-1-beta, IL-6, and TNF-alpha (Fiebich et al 2001).

Chondroprotective

In vitro data suggest that the active principles of *H. procumbens* inhibit not only inflammatory mediators but also mediators of cartilage destruction, such as matrix metalloproteinases, NO and elastase (Boje et al 2003, Schulze-Tanzil et al 2004). A study using an animal model confirmed a chondroprotective effect in which the tissue inhibitor of metalloproteinase-2 is involved (Chrubasik et al 2006).

Hypoglycaemic

Devil's claw extract produced a dose-dependent, significant reduction in the blood glucose concentrations of both fasted normal and fasted diabetic rats (Mahomed & Ojewole 2004).

OTHER ACTIONS

In vitro and in vivo evidence suggests that harpagoside may exhibit cardiac affects and lower blood pressure, heart rate and reduce arrhythmias (Fetrow & Avila 1999). As an extremely bitter herb, devil's claw is thought to increase appetite and bile production. Diterpenes extracted from the roots and seeds of devil's claw exhibited selective antiplasmodial (Clarkson et al 2003) and antibacterial activity (Weckesser et al 2007) in vitro, which may have future relevance in view of the increasing resistance to conventional antimalarials and antibiotics. One study showed that aqueous devil's claw extract can markedly delay the onset, as well as reduce the average duration, of convulsion in mice. Although not conclusive, it seems that the extract produces its anticonvulsant activity by enhancing GABAergic neurotransmission and/or facilitating GABAergic action in the brain (Mahomed & Ojewole 2006).

CLINICAL USE

Arthritis

Overall, evidence from clinical trials suggests that devil's claw is effective in the treatment of arthritis.

An observational study of 6 months' use of 3–9 g/day of an aqueous extract of devil's claw root reported significant benefit in 42–85% of the 630 people suffering from various arthritic complaints (Bone & Walker 1997). In a 12-week uncontrolled multicentre study of 75 patients with arthrosis of the hip or knee, a strong reduction in pain and the symptoms of osteoarthritis were observed in patients taking 2400 mg of devil's claw extract daily, corresponding to 50 mg harpagoside (Wegener & Lupke 2003). Similar results were reported in a 2-month observational study of 227 people with osteoarthritic knee and hip pain and non-specific low back pain (Chrubasik et al 2002) and a double-blind study of 89 subjects with rheumatic complaints using powdered devil's claw root (2 g/day) for 2 months, which also provided significant pain relief, whereas another double-blind study of 100 people reported benefit after 1 month (Bone & Walker 1997). A case report suggests that devil's claw relieved strong joint pain in a patient with Crohn's disease (Kaszkin et al 2004b). A single group open study of 8 weeks duration involving 259 patients showed statistically significant improvements in patient assessment of global pain, stiffness and function, and significant reductions in mean pain scores for hand, wrist, elbow, shoulder, hip, knee and back pain. Moreover, quality of life scores significantly increased and 60% of patients either reduced or stopped concomitant pain medication (Warnock et al 2007).

Comparisons with standard treatment have also been investigated. In 2000, encouraging results of a randomised double-blind study comparing the effects of treatment with devil's claw 2610 mg/day with diacerhein 100 mg/day were published (Leblan et al 2000). The study involved 122 people with osteoarthritis of the hip and/or knee and was conducted over 4 months. It found that both treatment groups showed similar considerable improvements in symptoms of osteoarthritis; however, those receiving devil's claw required fewer rescue analgesics.

One double-blind, randomised, multicentre clinical study of 122 patients with osteoarthritis of the knee and hip found that treatment with Harpadol (6 capsules/day, each containing 435 mg of cryoground powder of *H. procumbens*) given over 4 months was as effective as diacerhein (an analgesic) 100 mg/day (Chantre et al 2000). However, at the end of the study, patients taking Harpadol were using significantly fewer NSAIDs and had a significantly lower frequency of adverse events. In a 6-week study of only 13 subjects, similar benefits for devil's claw and indomethacin were reported (Newall et al 1996). A preliminary study comparing the proprietary extract Doloteffin with the COX-2 inhibitor rofecoxib reported a benefit with the herbal treatment but suggested that larger studies are still required (Chrubasik et al 2003b).

Previously reviews have concluded that there is moderate evidence of the effectiveness of *H. procumbens* in the treatment of osteoarthritis of the spine, hip and knee; however it is suggested, as with many herbal medicines, that evidence of effectiveness is not transferable from product to product and that the evidence is more robust for products that contain at least 50 mg of harpagoside in the daily dosage (Chrubasik et al 2003a, Gagnier et al 2004, Long et al 2001).

Recently two reviews have concluded that 'data from higher quality studies suggest that Devil's claw appeared effective in the reduction of the main clinical symptom of pain' (Brien et al 2006) and that the evidence of effectiveness was 'strong' for at least 50 mg of harpagoside as the daily dose (Chrubasik JE et al 2007). Nevertheless, 2 other recent reviews concluded that there was only 'limited evidence' (Ameye & Chee 2006) and 'insufficient reliable evidence' regarding the long term effectiveness of devil's claw (Gregory et al 2008).

The herb is Commission E approved as supportive therapy for degenerative musculoskeletal disorders (Blumenthal et al 2000) and ESCOP approved for painful osteoarthritis (ESCOP 2003).

Back pain

Several double-blind studies have reported benefit with devil's claw in people with back pain. A double-blind study of 117 people with back pain reported decreased pain and improved mobility after 8 weeks' treatment with devil's claw extract LI 174, known commercially as Rivoltan (Laudahn & Walper 2001). Use of the same extract provided significant pain relief after 4 weeks in another randomised, double-blind placebo-controlled study of 63 subjects with muscle stiffness (Gobel et al 2001). Similar results were reported in two double-blind studies of 118 people (Chrubasik et al 1996) and 197 people (Chrubasik et al 1999) with chronic lower back pain.

Devil's claw appears to compare favourably to conventional treatments. A 6-week double-blind study of 88 subjects comparing devil's claw to rofecoxib found equal improvements in both groups (Chrubasik et al 2003b) A follow-up of the subjects from that study who were all given devil's claw for 1 year found that it was well tolerated and improvements were sustained (Chrubasik et al 2005). In an open, prospective study, an unspecific lower back pain treatment with *Harpagophytum* extract and conventional therapy were found to be equally effective (Schmidt et al 2005).

Three recent reviews looking at the treatment of low back pain concluded that there is strong evidence for short-term improvements in pain and rescue medication for devil's claw products standardised to 50 and 100 mg harpagoside as daily doses (Chrubasik JE et al 2007, Gagnier et al 2006, 2007).

Devil's claw root is approved for relief of low back pain by ESCOP (ESCOP 2003).

Dyspepsia

Traditionally, devil's claw has also been used to treat dyspepsia and to stimulate appetite (Fisher & Painter 1996). The bitter principles in the herb provide a theoretical basis for its use in these conditions, although controlled studies are not available to determine effectiveness. The herb is Commission E (Blumenthal et al 2000) and ESCOP (2003) approved for dyspepsia and loss of appetite.

OTHER USES

Traditionally, the herb is also used internally to treat febrile illnesses, allergic reactions and to induce sedation, and topically for wounds, ulcers, boils and pain relief (Fisher & Painter 1996, Mills & Bone 2000), as well as for diabetes, hypertension, indigestion and anorexia (Van Wyk 2000).

DOSAGE RANGE

Musculoskeletal conditions

- Dried root or equivalent aqueous or hydroalcoholic extracts: 2–6 g daily for painful arthritis; 4.5–9 g daily for lower back pain.
- Liquid extract (1:2): 6–12 mL/day.
- Tincture (1:5): 2–4 mL three times daily.

It is suggested that devil's claw extracts with at least 50 mg harpagoside in the daily dosage should be recommended for the treatment of pain (Chrubasik 2004a, 2004b).

Digestive conditions (e.g. dyspepsia)

- Dosages equivalent to 1.5 g/day dried herb are used (Blumenthal et al 2000). It is suggested that devil's claw preparations be administered between meals, when gastric activity is reduced.

TOXICITY

The acute LD_{50} of devil's claw was more than 13.5 g/kg according to one study (Bone & Walker 1997). In a recent review of 28 clinical trials only a few reports on acute toxicity were found, whereas no reports on chronic toxicity had been reported. The review concluded that more studies for long-term treatment are needed (Vlachojannis et al 2008). An earlier review looking at 14 clinical trials had come to the same conclusion (Brien et al 2006).

ADVERSE REACTIONS

Devil's claw is a well tolerated treatment. In a recent review of 28 clinical trials it was found that only minor adverse events, mainly mild gastrointestinal symptoms (e.g. diarrhoea), occur in 3% of the patients. The incidence of adverse effects in the treatment groups was never higher than in the placebo groups for all 28 trials (Vlachojannis et al 2008).

SIGNIFICANT INTERACTIONS

Devil's claw has been found to moderately inhibit cytochrome P450 enzymes (CYP2C9, 2C19, 3A4) in vitro (Unger & Frank 2004), however, the clinical relevance of this is yet to be determined. In contrast to NSAIDs, devil's claw does not affect platelet function (Izzo et al 2005).

Warfarin

Rare case reports suggest that devil's claw may potentiate the effects of warfarin, but the reports are mostly inconclusive (Argento et al 2000, Heck et al 2000, Izzo et al 2005). Clinical testing would be required to confirm a possible interaction.

Anti-arrythmic drugs

Theoretical interaction exists when the herb is used in high doses; however, clinical testing is required to determine significance — observe patients taking concurrent antiarrythmics (Fetrow & Avila 1999).

CONTRAINDICATIONS AND PRECAUTIONS

Use cautiously in patients with gastric and duodenal ulcers, gallstones or acute diarrhoea, as devil's claw may cause gastric irritation (Blumenthal et al 2000).

PREGNANCY USE

Devil's claw is not recommended in pregnancy, as it has exhibited oxytocic activity in animals.

PRACTICE POINTS/PATIENT COUNSELLING

- Devil's claw reduces pain and inflammation and is a useful treatment in arthritis and back pain, according to controlled studies.
- The anti-inflammatory action appears to be different to that of NSAIDs and has not been fully elucidated. There is also preliminary evidence of a chondroprotective effect.
- Preliminary research suggests that it is best to take devil's claw between meals, on an empty stomach.
- Devil's claw appears to be relatively safe but should not be used in pregnancy and should be used with caution in people with ulcers or gallstones or in those taking warfarin.

PATIENTS' FAQs

What will this herb do for me?

Devil's claw is a useful treatment for arthritis and back pain. It may also increase appetite and improve digestion and dyspepsia.

When will it start to work?

Results from studies suggest that pain-relieving effects will start within 4–12 weeks reaching maximum pain relief after 3–4 months (Chrubasik S et al 2007, Thanner et al 2008).

Are there any safety issues?

Devil's claw should be used cautiously by people with gallstones, diarrhoea, stomach ulcers and those taking the drug warfarin. It is also not recommended in pregnancy.

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Dong quai

HISTORICAL NOTE Dong quai is an aromatic herb commonly used in Traditional Chinese Medicine (TCM). Its reputation is second to that of ginseng and is regarded as a 'female' remedy, or 'women's ginseng'. Used in combination with other herbs, dong quai is used to treat numerous menstrual disorders and menopausal symptoms, as well as abdominal pain, migraine headache, rheumatism and anaemia (Murray 1995). Dong quai (*Angelica sinensis*) is closely related to the European *Angelica archangelica*, a common garden herb and the flavouring in Benedictine and Chartreuse liqueurs.

COMMON NAME
Dong quai

OTHER NAMES
Chinese angelica, dang gui, women's ginseng, tang kuei

BOTANICAL NAME/FAMILY
Angelica sinensis (synonym: *Angelica polymorpha* var. *sinensis*) (family Apiaceae [Umbelliferae] — carrot family)

PLANT PART USED
Root

CHEMICAL COMPONENTS
Dong quai contains essential oil (0.4–0.7%) consisting of 45% ligustilide, n-butylphthalide, cadinene, carvacrol, safrole and isosafrol. The root also contains sucrose (40%) and various lactones and vitamins, together with phytosterols, ferulic acid and coumarins, including osthole, psoralen and bergapten (Micromedex 2003). Ferulic acid and ligustilide are considered to be the main active components (Dong et al 2005) and it has been suggested that assessment of total ferulic acid content provides a good measure of herbal quality (Lu et al 2005). High Performance Liquid Chromatography (HPLC) fingerprinting studies further suggest that active components are maintained better with whole roots than with prepared slices (Wu et al 2008). It is further suggested that the phenolic acids are the important contributors for antioxidant activity and that to maximise retention of volatile components, extracts should be prepared with 20% ethanol with extraction time less than 30 min (Huang et al 2008a).

MAIN ACTIONS
Nearly all studies investigating the pharmacological effects of dong quai have been conducted in vitro or in animals, so it is difficult to predict whether the observed effects are clinically significant.

Hormone modulation and uterine effects
Studies on the uterine effects of dong quai have produced variable results. A uterine relaxant effect has been attributed to the volatile oil, whereas a uterine stimulant effect has been attributed to an aqueous extract (Mills & Bone 2000). Animal experiments report that dong quai produces increased uterine excitability, with initial irregular, fast contractions, later slowing and becoming more regular (Zhu 1987).

Studies of dong quai's oestrogenic activity have also produced contradictory results. In vitro reports suggest that dong quai has weak oestrogen receptor-binding activity, producing up-regulation of progesterone receptor mRNA (Liu et al 2001), and stimulating oestrogen-dependent breast cancer cells independent of oestrogenic activity (Amato et al 2002). An aqueous extract of dong quai was found to stimulate the growth of both oestrogen receptor-positive and -negative breast cancer cells in vitro, suggesting both a weak oestrogen-agonistic activity and activity independent of oestrogen receptor-mediated pathways (Lau et al 2005). An in vivo study in ovariectomised rats found that dong quai had oestrogenic effects with stimulation of the uterine histoarchitecture with significant cornification in the vaginal epithelium and a reduction of serum LH concentration (Circosta et al 2006).

These findings are contrasted by a study using several different in vitro bioassays that found that dong quai did not have oestrogenic activity (Klein et al 2003), oestrogen receptor-binding activity or stimulate the growth of oestrogen-positive breast cancer cells and that it had neutral progestin activity (Zava et al 1998). Dong quai has also been reported to exhibit antioestrogenic and antiandrogenic activities in vitro (Rosenberg et al 2001).

Immunostimulant effect
It is reported that dong quai can counter the immunosuppressive effects of hydrocortisone in vivo (Mills & Bone 2000). Immunostimulation is further suggested by in vitro studies demonstrating enhanced cell-mediated immunity (Yang et al 2005) and up-regulation of IL-2 and IFN-gamma (Yang et al 2005), as well as non-specific lymphoproliferation (Wilasrusmee et al 2002). A polysaccharide from dong quai has also been found to enhance non-specific immunity while suppressing humoral immunity (Yang et al 2003).

Hepatoprotection
Dong quai is said to improve abnormal protein metabolism in people with chronic hepatitis or hepatic cirrhosis. Evidence comes from an in vivo study in which 5% dong quai was added to the daily diet of rats, resulting in enhanced metabolism, increased hepatic oxygen utilisation and increased glutamic acid and cysteine oxidation (Micromedex 2003). Dong quai has been found to have antioxidant activity (Wu et al 2004), as well as antiproliferative and proapoptotic activities in hepatic stellate cells in vitro, suggesting a potential antifibrotic action (Chor et al 2005).

Cardiac protection
Dong quai is reported to have a quinidine-like action, prolonging the cardiac refractory period and correcting atrial fibrillation (Fetrow & Avila 1999). An in vitro study of dong quai in conjunction with *Astragalus membranaceus* demonstrated protection against myocardial ischaemia-reperfusion injury (Yim et al 2000), while in vivo studies report prevention of atherosclerosis, dilation of coronary vessels and increased coronary blood flow (Mills & Bone 2000). In vivo and in vitro studies have also shown angiogenic effects (Lam et al 2008, Meng et al 2008) with enhanced expression of vascular endothelial growth factor (Shi et al 2007). A combined extract of dong quai and *Ligusticum chuanxiong* has been found to inhibit vascular smooth muscle cell proliferation in vitro (Hou et al 2005). In vivo studies in mice suggest that dong quai may protect against doxorubicin-induced chronic cardiotoxicity without compromising doxorubicin's antitumour activity (Xin et al 2007).

Anticoagulant and antiplatelet effects

Dong quai has been shown to have potent anticoagulant effects, as well as haemostatic effect related to promoting platelet aggregation (Yang et al 2002b). In a controlled trial, an IV preparation of dong quai was found to prolong prothrombin times significantly more than IV dextran in a group of 96 patients admitted with ischaemic stroke (Micromedex 2003). Dong quai has also been shown to significantly inhibit platelet activation, relieve vascular endothelial cell injury and improve microcirculation in patients with ulcerative colitis (Dong et al 2004). Ferulic acid, found in dong quai, has been reported to inhibit the aggregation of platelets in blood and retard platelet release of serotonin and adenosine diphosphate. *Angelica sinensis* has a lower coumarin content than other *Angelica* species.

Anticarcinogenic

Polysaccharides from dong quai have been shown to possess antitumour effects in experimental in vivo tumour models and inhibitory effects on invasion and metastasis of in vitro hepatocellular carcinoma cells (Shang et al 2003). An acetone extract of dong quai was found to inhibit proliferation of human cancer cells in vitro via induction of cell cycle arrest and apoptosis (Cheng et al 2004). There is evidence to suggest that a chloroform extract of dong quai suppresses growth of malignant brain tumour cells in vitro, as well as suppressing growths of malignant brain tumours of rat and human origin and shrinking the volumes of in situ glioblastoma multiforme, significantly prolonging survivals in vivo (Tsai et al 2005). An in vitro study suggests that the three main phthalides might have anticancer potential and that they may work in synergy with other compounds to produce an even stronger antitumour effect (Kan et al 2008).

Dong quai has been shown to protect against the cytotoxicity of cyclophosphamide on haematopoietic and gastrointestinal tissues in mice studies which further suggest that this may occur in part through the down regulation of vascular endothelial growth factor (Hui et al 2006). In vitro and in vivo studies in mice have also found that lipid soluble extracts of dong quai inhibit tumour growth through a similar mechanism (Lee et al 2006).

Neuroprotection

Dong quai has been found to be effective in treating acute cerebral infarction. In a case series of 1404 patients with acute cerebral infarction, of whom 692 were treated with dong quai injection, 390 with compound salvia and 322 with low-molecular-weight dextran injection, the group treated with dong quai were found to have significantly better neurological function and a larger reduction of infarcted area than the other groups (Liu Y-M et al 2004).

Bak Foong Pills, a combination Chinese herbal formula that contains dong quai and other herbs such as *Panax ginseng* and *Glycyrrhiza uralensis*, has been found to have a neuroprotective action, suggesting that these herbs may be used in the treatment of neurodegenerative diseases, such as Parkinson's disease (Jia et al 2005, Rui et al 2005). A multiherbal formula (Guibi-tang) containing dong quai has also been shown to improve learning and memory, and to increase the proliferation of hippocampal cells in rats (Oh et al 2005). An aqueous extract of three herbs, including dong quai, has been found to have a neuroprotective action and improve cognitive function in an animal model of vascular dementia (Lin et al 2005), and a multiherbal combination (Danggui-Shaoyao-san) has been found to improve memory and modulate monoamine neurotransmitter metabolism suggesting a possible use for treating senile dementia and Alzheimer's disease (Kou et al 2005). This is supported by in vitro studies, which found that dong quai extract prevented the neurotoxicity induced by Amyloid beta (A-beta) associated oxidative stress (Huang et al 2008b).

Gastroprotection

Polysaccharides derived from dong quai have been found to have a protective effect on colon injury in animal models through promotion of growth factors, decreasing oxygen free radicals and some anti-inflammatory effects (Liu S-P et al 2004, Wong et al 2008), as well as relieving the inflammation reaction and colon injury in immunological colitis in rats (Liu et al 2003a, 2003b). A polysaccharide containing extract of dong quai was also shown to promote migration and proliferation of normal gastric epithelial cells and enhance gastric ulcer healing in animal models (Ye et al 2003).

Anti-inflammatory

Dong quai is reported to be used to treat radiation pneumonitis in humans receiving treatment for thoracic cancer. In vivo mouse studies suggest that this action may be due to dong quai effectively down-regulating TNF-alpha and TGF-beta1 in irradiated lung tissue (Xie et al 2006). An aqueous extract of dong quai has also been found to protect against lethal endotoxaemia and experimental sepsis in part by attenuating systemic accumulation of late proinflammatory cytokines (Wang et al 2006).

OTHER ACTIONS

A preparation containing polysaccharides extracted from dong quai has been shown to have a radioprotective effect in mice (Mei 1988, Sun et al 2005), as well as an analgesic action in rats (Yue et al 2002).

An in vivo study has shown that dong quai in conjunction with astragalus reduced the deterioration of renal function and histologic damage in an animal model of nephrotic syndrome (Wang et al 2004). Dong quai has also been found to alleviate bleomycin-induded pulmonary fibrosis in rats (Chai et al 2003).

Dong quai promotes melanocytic proliferation, melanin synthesis and tyrosinase activity, suggesting a use in the treatment of skin pigmentation (Deng & Yang 2003).

An aqueous extract of dong quai has also been found to directly stimulate the proliferation and activity of human osteoprecursor cells in a dose-dependent manner in vitro (Yang et al 2002a).

The essential oil of dong quai has been found to have an anxiolytic action similar to diazepam in a mouse model of anxiety (Chen et al 2004).

In a rat model of iron deficiency anaemia, a dong quai polysaccharide–iron complex was found to be as effective as an iron-supplementing agent as well as supplementing blood and activating blood circulation (Wang et al 2007).

Various other in vitro and in vivo studies provide some evidence for antispasmodic, anti-allergic and antianaemic effects (Micromedex 2003).

CLINICAL USE

While dong quai has been used widely, in a clinical setting it is most often used in combination with multiple other Chinese herbs as part of traditional preparations and very little clinical research has been performed on it as a sole treatment making it difficult to assess its individual contribution to any clinical effects.

Gynaecological use

Orally, dong quai has been traditionally used in combination with other herbs for gynaecological ailments, including menstrual cramps, irregularity, retarded flow, weakness during the menstrual period and symptoms of menopause (Fisher & Painter 1996). Very little clinical research has been conducted to determine its effectiveness as sole treatment in these indications.

In a 12-week randomised, placebo-controlled trial in 55 postmenopausal women, a combination of dong quai and chamomile was found to significantly reduce hot flushes and improve sleep disturbances and fatigue. Another double-blind, randomised, placebo-controlled clinical trial of 71 women using dong quai as a single agent (4.5 g/day) found no differences between groups in the number of vasomotor flushes, endometrial thickness or vaginal cells over a 24-week period (Hirata et al 1997).

It is suggested that dong quai may have some efficacy for premenstrual syndrome when used in traditional Chinese multiherbal formulas (Hardy 2000), and an uncontrolled trial has suggested the possible benefit of uterine irrigation with dong quai extract for infertility due to tubal occlusion (Hardy 2000).

OTHER USES

In TCM, dong quai is used to strengthen the heart, lung and liver meridians and harmonise the blood. It is used to regulate menstruation, treat amenorrhoea, dysmenorrhoea, headache, constipation, abdominal pain and palpitations.

Traditionally, dong quai is considered a 'hot' herb and is not used in conditions associated with 'heat', according to these prescribing systems.

DOSAGE RANGE

- Decoction of dried root: 4.5–9 g/day.
- Liquid extract (1:2): 4.5–8.5 mL/day.

ADVERSE REACTIONS

Furanocoumarins, such as bergapten and psoralen, which are in dong quai have been widely studied for their phototoxicity; however, only *Angelica gigas* (Korean angelica) has been demonstrated to cause photodermatitis.

Safrole, found in the volatile oil, is a potential carcinogen; however, no specific cases of carcinogenesis have been reported (Micromedex 2003).

High doses of dong quai volatile oil have been reported to cause nephrosis in rats but there are no reports in humans (Zhu 1987).

SIGNIFICANT INTERACTIONS

An aqueous extract of dong quai has been found to increase CYP2D6 and 3A in vitro which may lead to potential drug interactions (Tang et al 2006).

Warfarin

Case reports suggest that the elevations in prothrombin and INR may occur when dong quai is used with warfarin (Heck et al 2000, Page & Lawrence 1999) — use caution if used concurrently with warfarin.

CONTRAINDICATIONS AND PRECAUTIONS

Because dong quai may have oestrogenic effects, women with hormone-sensitive tumours, endometriosis and uterine fibroids should avoid using dong quai.

Traditional contraindications include diarrhoea due to weak digestion, haemorrhagic disease, heavy periods, first trimester of pregnancy and acute infections such as cold or flu (Zhu 1987).

PREGNANCY USE

Dong quai may stimulate uterine contractions and is therefore contraindicated in pregnancy (Mills & Bone 2000).

PRACTICE POINTS/PATIENT COUNSELLING

- Dong quai is a popular Chinese medicine used widely to relieve menopausal symptoms; however, controlled trials in humans are lacking. In practice, dong quai is prescribed together with other herbs and may be effective when used in this way.
- Evidence of oestrogenic activity is contradictory.
- Care is required in people using drugs that affect blood clotting.
- Dong quai is generally safe when used appropriately.

PATIENTS' FAQs

What will this herb do for me?

Dong quai has a long history of use as a women's tonic. Although conclusive evidence is lacking, dong quai is used in conjunction with other herbs to assist in menopausal and menstrual complaints, and may be effective when used in this way.

When will it start to work?

It is difficult to predict from the available scientific research.

Are there any safety issues?

Dong quai appears to be relatively safe but care should be taken in people using drugs that affect blood clotting or in pregnancy and conditions that are hormone sensitive.

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Dunaliella salina

HISTORICAL NOTE Microalgae is a nutrient-dense natural food and medicine that has been used for thousands of years by the Aztecs, some African and Asian peoples and South Pacific islanders. It has been suggested that gram-for-gram microalgae is the most nutrient-dense food on earth (Passwater & Solomon 1997) with minimal indigestible structures in contrast to higher plants or animals, which typically have less than half their dry weight being nutritionally useful (Bruno 2001). Examples of edible algae include *Spirulina*, *Chlorella* and *Dunaliella salina*. The last may be the most nutrient dense of the three, primarily due to its extremely high concentration of carotenoid antioxidants. The high carotenoids content is believed to impart a pink colouring to salt lakes where the microalgae flourish. The colour is amplified through the food chain to give the pink colour to brine shrimp and flamingos (Skinner 2008).

COMMON NAME
Dunaliella salina

BOTANICAL NAME/FAMILY
Dunaliella salina and *Dunaliella bardawil* are considered to be the same species (Borowitzka & Borowitzka 1988).

OTHER NAMES
Red marine phytoplankton (microalgae)

PLANT PARTS USED
Dunaliella salina is a marine phytoplankton that is a unicellular, biflagellate, soft walled, green algae that lives in salt-water lakes and coastal waters. As a phytoplankton, *D. salina* can be considered a whole plant; yet, it has a soft cell membrane that makes it easily digestible, compared with other microalgae that have hard cell walls (Ben-Amotz & Avron 1983). *D. salina* is one of the most salt-tolerant life forms known and is found in hypersaline waters generally >20% (salt lakes and evaporation ponds of salt works). It has a wide tolerance to environmental extremes, especially salinity, pH (pH 1 to pH 11), temperature (>45°C) and high UV exposure (Borowitzka & Borowitzka 1988). To cope with these extreme environments, *D. salina* produces very high levels of carotenoids in the chloroplast (organelles that conduct photosynthesis) as well as maintaining a high mineral content.

CHEMICAL COMPONENTS
D. salina contains a range of macro- and micronutrients, including amino acids, lipids and fatty acids, carbohydrates, chlorophyll, vitamins and minerals along with very high levels of carotenoids. As a phytoplankton that grows in seawater, *D. salina* is rich in many trace minerals. *D. salina* is also extremely high in carotenoids and while it contains over 500 different carotenoids, including alpha-carotene, lutein, zeaxanthin and cryptoxanthum, it is the richest known natural source of beta-carotene (USDA 2005), which it can make up to 8% of its dry weight (Ben-Amotz & Avron 1983). *D. salina* is therefore commonly used as a source of natural beta-carotene or mixed carotenoids in nutritional supplements (see Beta-carotene monograph).

Unlike synthetic (all-*trans*) beta-carotene, the beta-carotene from *D. salina* is composed of near equal amounts of the all-*trans* and 9-*cis* stereoisomers, which differ in their physicochemical features and antioxidative activity. The 9-*cis* isomer is considered to be one of nature's most powerful antioxidants, thus *D. salina* provides much greater bioavailability and antioxidant activity than synthetic beta-carotene supplements (Ben-Amotz & Levy 1996, Ben-Amotz et al 1989, Stahl et al 1993) (see *Beta-carotene* monograph).

It is believed that exposure to reactive oxygen species (ROS) triggers extensive carotenoid accumulation in *D. salina* (Ye et al 2008) and there are a number of biotechnology processes aimed at extracting its natural beta-carotene content (Lamers et al 2008, Raja et al 2007a). As a supplement, *D. salina* can be produced in either the whole dried (unwashed) form that contains high levels of minerals or a washed (desalinated) form that has higher carotenoid levels and lower mineral levels. Recently, advances in production technology have allowed the whole dried

D. salina biomass with its full range of nutrients and minerals to become commercially available in supplement form (Tracton & Bobrov 2005).

MAIN ACTIONS

Antioxidant and anti-inflammatory

Animal studies suggest that natural beta-carotene from *D. salina* can protect rats against CNS oxygen toxicity (Bitterman et al 1994), whole body irradiation (Ben-Amotz et al 1996) and gastrointestinal inflammation (Lavy et al 2003, Takenaka et al 1993). It is suggested that the gastric cytoprotective effect may depend on the amount of beta-carotene accumulated. A study that fed rats with diets containing up to 0.1% beta-carotene for 2 weeks using either dry *D. salina*, purified natural beta-carotene from *D. salina* or synthetic beta-carotene found that the rats showed higher accumulations of the algal beta-carotene than of the synthetic all-*trans* beta-carotene and that the *D. salina* and algal beta-carotene supplementation both significantly decreased the gastric mucosal lesions after water immersion stress, while synthetic beta-carotene did not (Takenaka et al 1993).

Cytoprotection

Animal studies suggest that supplementation with *D. salina* has hepatoprotective effects and can protect rats against laboratory models of liver toxicity to a significantly greater degree than synthetic beta-carotene. This is most likely due to the presence of various isomeric forms of carotene and other oxygenated carotenoids (Chidambara Murthy et al 2005, Vanitha et al 2007). *D. salina* supplementation has also been found to protect rats against laboratory-induced fibrosarcoma (Raja et al 2007b). Further studies have shown that prefeeding rats with *D. salina* ameliorated acid-induced enteritis (Lavy et al 2003). A double-blind trial in humans found that a single dose of natural beta-carotene from *D. salina* reduced the severity, but not the incidence, of postprocedural pancreatitis after endoscopic retrograde cholangiopancreatography (ERCP) (Lavy et al 2004).

Anti-atherogenic

Supplementation with *D. salina* powder inhibited atherogenesis in animal models using high-fat diet-fed LDL receptor knockout mice. Reductions of plasma cholesterol of 40–63% and atherosclerotic lesions of 60–83% along with reduced liver fat accumulation, liver inflammation and mRNA levels of inflammatory genes were also observed. By administrating *D. salina* powder containing different levels of 9-*cis* and all-*trans* beta-carotene isomers, these effects were shown to be 9-*cis*-dependent (Harari et al 2008).

Photoprotection

The red, orange and yellow colours of *D. salina* preferentially absorb UV light, therefore, ingestion of the microalgae adds pigmentation to the skin which helps to absorb UV light and reduce the effects of UV-induced erythema (sunburn) (Heinrich et al 2003). The beta-carotene in *D. salina* demonstrates photoprotective activity in plant cells and recent studies show that it has a similar effect on human skin (Heinrich et al 2003, Stahl et al 2000).

OTHER ACTIONS

Detoxification

D. salina contains chlorophyll along with other vitamins and minerals such as selenium and magnesium that are believed to aid in detoxification (Murray 1997). A small cohort study recently found that 14 weeks of supplementation with 3 g/day of *D. salina* powder produced marked reductions in hair tissue levels of various heavy metals. These findings now await further confirmation in controlled trials (Bobrov et al 2008).

Antibacterial

A study on the antimicrobial activity of different pressurised liquid extracts obtained from *D. salina* found 15 different volatile compounds as well as several fatty acids (mainly palmitic, alpha-linolenic and oleic acids) may be responsible for the observed antibacterial activity (Herrero et al 2006).

Antiproliferative

An ethanol extract of *D. salina* has been found to have antiproliferative effects and induce cell cycle G0/G1 arrest and apoptosis of human lung cancer cells (Sheu et al 2008).

Chemoprevention

There has been considerable research into carotenoids and chemoprevention. Many studies have shown the correlation between high intakes of natural beta-carotene from food and a decreased risk in the carcinogenesis of stomach, prostate and breast cancers (see Beta-carotene monograph). It is likely that natural beta-carotene from *D. salina* has different biological activity from synthetic beta-carotene — while synthetic beta-carotene has been shown to increase the risk of lung cancer in some populations, this has not been demonstrated with natural beta-carotene. As such, it is possible that long-term usage of *D. salina* may also decrease the risk of various cancers; however, this has yet to be investigated.

CLINICAL USE

D. salina is nature's richest source of natural beta-carotene and as such has similar uses to beta-carotene. To date, most of the clinical research on *D. salina* has been conducted with beta-carotene-containing extracts rather than the whole organism. This research suggests that potential benefits of supplementation with *D. salina* include prevention of cancer and cardiovascular disease, protection against sun damage and photosensitivity, supporting healthy eye, skin and immune function, providing benefits in asthma, macular degeneration and promotion of overall health and wellbeing (see *Beta-carotene* monograph).

Antioxidant protection

Human studies on *D. salina* extracts suggest many positive clinical effects, mainly due to its antioxidant activity. This is supported by the results of two

studies involving supplementation with a *D. salina* extract containing 60 mg/day of beta-carotene for 3 weeks in patients with non-insulin dependent diabetes mellitus (NIDDM). These studies found a reduction in oxidative injury (Levy et al 1999) along with normalisation of LDL oxidation (Levy et al 2000). Further support for the clinical benefits from the antioxidant properties of *D. salina* come from a study of 709 children with long-term exposure to radiation during and after the Chernobyl accident which found that 3-month supplementation with 40 mg of beta-carotene powder from *D. salina* reduced serum markers for oxidisation and acted as a lipophilic antioxidant and radioprotector (Ben-Amotz et al 1998).

Photoprotection

D. salina extracts protect the skin from sunburn and sun damage due to increased protective pigmentation of the skin along with reduced susceptibility to sunburn, according to a clinical study (Heinrich & Tronnier 1998, Stahl et al 1993). The placebo-controlled ($n = 24$) trial found 12 weeks of supplementation with 24 mg/day of *Dunaliella*-derived carotenoids significantly increased protection from sunburn (Heinrich et al 2003).

Exercise-induced asthma

A double-blind, placebo-controlled trial involving 38 subjects found that 1-week supplementation with *D. salina* provided a protective effect for patients with exercise-induced asthma (Neuman et al 1999).

DOSAGE RANGE

1–3 g of whole dried *D. salina* powder (which contains around 1–2% beta-carotene) when taken as a supplement.

ADVERSE REACTIONS

D. salina is classified as an edible species of microalgae. While no human toxicology studies have been carried out, there are no reported adverse effects from consumption of the whole microalgae or beta-carotene extract from *D. salina* in human clinical studies. An orange or yellow skin colouration (carotenodermia) may become evident after a few months of consumption but this is harmless and reversible on discontinuation (see *Beta-carotene* monograph).

SIGNIFICANT INTERACTIONS

No known interactions at this time.

PREGNANCY USE

While *D. salina* is considered safe, there is insufficient information to guide its use in pregnancy.

PATIENTS' FAQs

What will it do for me?

D. salina provides a source of natural beta-carotene and minerals that may promote energy and vitality, enhance skin health and appearance and assist in healthy ageing. As a rich source of beta-carotene, *D. salina* acts to supplement vitamin A levels without the risk of vitamin A toxicity. It may be used to assist in maintaining healthy skin, eyes and immune function, prevention of cancer and cardiovascular disease and reducing oxidative stress. *D. salina* may also provide photoprotection, detoxification of heavy metals and protective effect for patients with exercise-induced asthma.

When will it start to work?

Effects may be observable within 1 week but may take up to 3 months to obtain full benefits, while benefits of long-term supplementation on disease prevention may take many years to become evident. *D. salina* should be taken with meals or other dietary fats to increase the bioavailability of carotenoids.

Are there any safety issues?

D. salina is considered non-toxic. Large doses over long periods of time may produce carotenodermia, which is a harmless and reversible yellow-orange discolouration of the skin.

PRACTICE POINTS/PATIENT COUNSELLING

- *D. salina* is a marine phytoplankton that grows in extreme environments and is nature's richest source of natural beta-carotene.
- Dunaliella is a 'whole-food' supplement that provides a range of trace minerals and other nutrients that provide antioxidant, anti-inflammatory and photoprotection activity.
- Supplementation with *D. salina* may assist in prevention of a range of conditions including cardiovascular disease, some cancers and exercise-induced asthma.
- The antioxidants in *D. salina* may provide some protection against exposure to the sun and other sources of radiation.

STORAGE

D. salina should be stored in airtight containers or capsules away from direct sunlight, as carotenoids will oxidise on exposure to air and light.

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Echinacea

HISTORICAL NOTE Echinacea was first used by Native American Sioux Indians centuries ago as a treatment for snakebite, colic, infection and external wounds, among other things. It was introduced into standard medical practice in the USA during the 1800s as a popular anti-infective medication, which was prescribed by eclectic and traditional doctors until the 20th century. Remaining on the national list of official plant drugs in the USA until the 1940s, it was produced by pharmaceutical companies during this period. With the arrival of antibiotics, echinacea fell out of favour and was no longer considered a 'real' medicine for infection. Its use has re-emerged, probably because we are now in a better position to understand the limitations of antibiotic therapy and because there is growing public interest in self-care. The dozens of clinical trials conducted overseas have also played a role in its renaissance.

COMMON NAME
Echinacea

OTHER NAMES
E. angustifolia — American coneflower, black sampson, black susans, coneflower, echinaceawurzel, Indian head, kansas snakeroot, purple coneflower, purpursonnenhutkraut, racine d'echinacea, *Rudbeckia angustifolia* L., scurvy root, snakeroot

E. purpurea — *Brauneria purpurea* (L.) Britt., combflower, purple cone flower, red sunflower

Rudbeckia purpurea L. — *E. pallida*, *Brauneria pallida* (Nutt.) Britt., pale coneflower, Rudbeckia pallida Nutt.

BOTANICAL NAME/FAMILY
Echinacea species (family Asteraceae [Compositae])

The name 'echinacea' generally refers to several different plants within the genus — *E. purpurea*, *E. pallida* and *E. angustifolia*.

PLANT PARTS USED
Root, leaf and aerial parts

CHEMICAL COMPONENTS
The most important constituents with regard to pharmacological activity are the polysaccharides, caffeic acid derivatives, alkylamides, essential oils and polyacetylenes, although there are other potentially active constituents, as well as a range of vitamins, minerals, fatty acids, resins, glycoproteins and sterols (Pizzorno & Murray 2006). Cynarin, a potential immunosuppressant and CD28 ligand, was also identified in *E. purpurea* (Dong et al 2006). Constituent concentrations vary depending on the species, plant part and growing conditions. With regard to the final chemical composition of an *Echinacea*-containing product, the drying and extraction processes further alter chemical composition.

Pharmacokinetics

The absorption of *E. purpurea* alkylamides from lozenges is rapid and linear (Guiotto et al 2008). A clinical study with healthy volunteers showed that following ingestion of tablets containing ethanolic echinacea extract, alkylamides were detectable in plasma 20 min after ingestion, whereas caffeic acid derivatives were not detectable in the plasma at any time after tablet ingestion (Matthias et al 2005a). A further study by the same authors showed that there was no significant difference in the bioavailability of alkylamides from a liquid and solid oral dosage form of an echinacea product (mixture of *E. purpurea* and *E. angustifolia*), with T_{max} reached at 20 and 30 min, respectively (Matthias et al 2007b). Two other studies reported that 30 to 45 min following administration of *E. purpurea* products (Echinaforce tincture, tablets, spray) containing milligram amounts of alkylamides, plasma concentrations of alkylamides of about 0.07–0.40 ng/mL were recorded (Woelkart et al 2006, 2008), and effects on the immune markers observed 23 h after oral administration (Woelkart et al 2006). Furthermore, tetraene alkylamides, present in *E. angustifolia* and *E. purpurea*, have been found to be metabolised by CYP450 enzymes (Matthias et al 2005b). In addition, the metabolism of tetraene alkylamides can be significantly decreased by monoene alkylamides that are only found in *E. angustifolia* (Matthias et al 2005b).

MAIN ACTIONS

Due to the wide assortment of chemical constituents found in echinacea, it has varied pharmacological effects.

Immunomodulator

Experimental results suggest that echinacea functions more as a modulator of the immune response rather than as a pure immune stimulant. It appears that in resting cells, an immune stimulus produces a faster response when the cells have been exposed to echinacea, whereas in overstimulated cells echinacea reduces the immune response. The immunomodulator activity of echinacea has been the subject of countless studies and appears to be the result of multiple mechanisms.

Overall, the fresh-pressed leaf juice of *E. purpurea* and alcoholic extracts of the roots of *E. pallida*, *E. angustifolia* and *E. purpurea* have been shown to act mainly on non-specific cellular immunity (Blumenthal et al 2000). It was reported that no one single constituent is responsible for the herb's immunomodulating action, with the most important elements being polysaccharides, glycoproteins, alkamides and flavonoids (Ernst 2002). A recent study suggests that water-soluble rather than lipophilic constituents are responsible for the immunostimulatory activity (Pillai et al 2007).

Macrophage activation has been well demonstrated, as has stimulation of phagocytosis (Barrett 2003, Bauer et al 1988, Groom et al 2007, Pugh et al 2008, Zhai et al 2009). Orally administered root extracts of echinacea have produced stronger effects on phagocytosis than aerial parts, with *E. purpurea* roots producing the greatest effect, followed by that of *E. angustifolia* and *E. pallida* (Pizzorno & Murray 2006).

The activation of polymorphonuclear leucocytes and natural killer (NK) cells and increased numbers of T-cell and B-cell leucocytes have been reported (Groom et al 2007, Zhai et al 2007a).

Echinacea stimulates cytokine (Altamirano-Dimas et al 2007, Brush et al 2006, Dong et al 2006, 2008, Farinacci et al 2008, Sharma et al 2006, Zhai et al 2007a, Zwickey et al 2007) and chemokine production (Wang et al 2006, 2008). Moreover, various echinacea species stimulate NO production in vitro (Classen et al 2006, Sullivan et al 2008).

Contradictory results were obtained for TNF-alpha production. In one study, echinacea significantly increased TNF-alpha production (Senchina et al 2006), whereas no effects on TNF-alpha were observed for all echinacea species in another study (McCann et al 2007), and in a third study, NFkappaB expression and TNF-alpha levels decreased in non-stimulated macrophages following echinacea treatment (Matthias et al 2007a).

In lipopolysaccharide-stimulated (LPS – endotoxin) cells, echinacea inhibited NFkappaB, TNF-alpha, NO and cytokine production, with different alkylamides exerting different effects (Matthias et al 2007a, 2008, Raduner et al 2006, Sasagawa et al 2006, Stevenson et al 2005, Woelkart et al 2006, Zhai et al 2007a).

Research in human subjects has produced conflicting results, with some studies showing that echinacea stimulates non-specific immunity and others showing no significant effect (Roesler et al 1991, Schwarz et al 2002).

Anti-inflammatory

Recent research has shown that alcohol extracts of all three echinacea species (*E. angustifolia*, *E. purpurea* and *E. pallida*) exert significant anti-inflammatory activity (Raso et al 2002, Zhai et al 2008). The result is due to multiple constituents acting with multiple mechanisms. The alkylamide fraction inhibits nitric oxide synthase (iNOS) and the caffeic acid fraction enhances arginase activity (Zhai et al 2008). In vivo tests further identify anti-inflammatory effects also for *E. angustifolia* and *E. pallida* when applied topically (Speroni et al 2002, Tragni et al 1985, Tubaro et al 1987).

COX-1/COX-2

Alkylamides from the roots of *E. purpurea* partially inhibit both COX-1 and COX-2 isoenzymes thus decreasing prostaglandin E2 levels (Clifford et al 2002, LaLone et al 2007, Raman et al 2008). Several alkylamides isolated from a CO_2 extract of the roots of *E. angustifolia* have been shown to inhibit COX-2-dependent prostaglandin E_2 formation although COX-2 mRNA and protein expression was not inhibited, but rather increased (Hinz et al 2007).

Cannabinoid & TRPV1 receptor interaction

It has been further identified that alkamides from echinacea modulate TNF-alpha mRNA expression in human monocytes/macrophages via the cannabinoid type 2 (CB2) receptor, thus

Clinical note — Echinacea and cannabinoid receptors

Alkylamides found in echinacea show a structural similarity with anandamide, an endogenous ligand of cannabinoid receptors. Cannabinoid type-1 (CB1) and CB2 receptors belong to G-protein coupled receptors. CB2 receptors are believed to play an important role in various processes, including metabolic dysregulation, inflammation, pain and bone loss. Compounds such as cannabinoids, which act on these receptors, are becoming more and more popular as they represent new targets for drug discovery. A well-known plant cannabinoid is delta-9-tetrahydrocannabinol, a constituent of *Cannabis sativa*.

identifying a possible mode of action for its immunomodulatory activity (Raduner et al 2006, Woelkart & Bauer 2007). Two alkylamides, which bind to the CB2 receptor more strongly than endogenous cannabinoids and activate it, have been classified as a new class of cannabinomimetics (Gertsch et al 2006). It was found that some of the alkylamides in echinacea self-assemble into micelles in aqueous solution which then determines their binding to the CB2 receptor (Raduner et al 2007). However, ketoalkenes from *E. pallida* did not interact with cannabinoid receptors (Egger et al 2008).

Ethanol extracts from echinacea roots showed potent agonist activity on TRPV1, a mammalian pain receptor. The compounds involved in the TRPV1 receptor activation differed from those involved in the inhibition of prostaglandin E2 production (Birt et al 2008).

Immunological adjuvants

In vitro studies in human lymphocytes activated with different lectins showed that using *E. purpurea* root extract in addition to individual lectins increased lymphoproliferation, which would suggest adjuvant activity (Chaves et al 2007). In mice, no adjuvant activity was detected for lipophilic, neutral and acidic extracts of echinacea (Gaia Herbs) (Ragupathi et al 2008).

Antiviral

Extracts of eight taxa of the genus *Echinacea* were found to have antiviral activity against herpes simplex virus (HSV)-1 in vitro when exposed to visible and ultraviolet A (UVA) light (Binns et al 2002). Antiviral activity was confirmed for *E. purpurea* extracts in 2008, with evidence suggesting that polyphenolic compounds other than the known HIV inhibitor, cichoric acid, may also be involved (Birt et al 2008).

Antifungal activity

Hexane extracts of echinacea have phototoxic antimicrobial activity against fungi (Binns et al 2000). The extracts inhibited growth of yeast strains of *Saccharomyces cerevisiae*, *Candida shehata*, *C. kefyr*, *C. albicans*, *C. steatulytica* and *C. tropicalis*.

OTHER ACTIONS

Traditional

Herbalists consider echinacea to have lymphatic, blood cleansing and wound healing actions.

Antioxidant

Free radical scavenging activity can be attributed to numerous antioxidant constituents found in echinacea, such as vitamin C, beta-carotene, flavonoids, selenium and zinc. One in vitro study reported that the antioxidant activity exerted by echinacea tincture was significantly greater than that observed for *Ginkgo biloba* (Masteikova et al 2007).

Anaesthetic

The alkylamides exert a mild anaesthetic activity, which is typically experienced as a tingling sensation on the tongue (Pizzorno & Murray 2006).

Apoptosis

Apoptosis, or programmed cell death, is a physiological, active cellular suicide process that can be modulated by various stimuli, including hormones, cytokines, growth factors and some chemotherapeutic agents. Research has been undertaken with the three clinically used *Echinacea* spp., several key constituents and different herbal fractions to investigate mechanisms of action, strength of activity and specificity of effect.

The *n*-hexane extracts of all three *Echinacea* spp. exert cytotoxic effects on human pancreatic and colon cancer cells in a concentration- and time-dependent manner, with *E. pallida* being the most active species (Aherne et al 2007). The effects were partially due to apoptosis by significantly increasing caspase-3/7 activity (Chicca et al 2007, 2008). Cytotoxic effects of the *n*-hexane extract of *E. angustifolia* on lung cancer cells have also been reported (Ramirez-Erosa et al 2007). However, in comparison to other herbal medicines such as wild yam and dichora root, echinacea exhibits only weak tumouricidal effects (Mazzio & Soliman 2008).

Isolated hydroxylated polyacetylenes and polyenes (more hydrophilic) from *E. pallida* are less cytotoxic than the more hydrophobic compounds (Pellati et al 2006).

It has been shown that the effects of isolated constituents on cell proliferation vary. In cervical and breast cancer cells treated with doxorubicin and *E. purpurea* extract or isolated echinacea constituents (i.e. cynarin, chicoric acid), the ethyl acetate fraction of echinacea extract and chicoric acid increased breast cancer cell growth and cynarin enhanced the growth of cervical cancer cells. However, cynarin showed antiproliferative effects on breast cancer cells (Huntimer et al 2006).

Chemoprevention

Several experimental studies with mice have found that treatment with echinacea reduces the incidence of tumour development (Brousseau & Miller 2005, Hayashi et al 2001, Miller 2005). Most research has been conducted with *E. purpurea*. In a study with gamma-irradiated mice, *E. purpurea* was able to

show radioprotection (use before radiation) as well as radio-recovery effectiveness (Abouelella et al 2007). One study reported that *E. angustifolia* can stimulate mammary epithelial cell differentiation (Starvaggi Cucuzza et al 2008).

Antiparasitic

Aqueous extracts of echinacea showed activity against gastrointestinal nematodes in goats and pigs (Lans et al 2007).

CLINICAL USE

Clinical trials using echinacea have used various preparations, such as topical applications, homeopathic preparations, injectable forms and oral dose forms, characteristics that should be noted when reviewing the data available. Overall, the majority of clinical studies performed in Europe have involved a commercial product known as Echinacin (Madaus, Germany), which contains the fresh-pressed leaf juice of *E. purpurea* stabilised in ethanol.

Upper respiratory tract infections

Overall, clinical studies support the use of echinacea in upper respiratory tract infections (URTIs), such as bacterial sinusitis, common cold, influenza-like viral infections and streptococcal throat. Evidence most strongly supports the use of echinacea in adults as an acute treatment, with some evidences showing that it is also useful as a means of reducing the natural incidence of the common cold. With regard to acute treatment, evidence is most consistent for the *E. purpurea* preparations (aerial parts and root) and for best clinical effects, treatment should be commenced at the first signs of infection (Linde et al 2006, Schoop et al 2006a, Woelkart et al 2008a). Preparations from *E. angustifolia* and *E. pallida* need further controlled clinical trials to provide better evidence for efficacy as acute treatments (Woelkart et al 2008b). As preventative treatment, *E. purpurea* (pressed juice) and *E. angustifolia* (alcoholic extract) show the most promise although further investigation is still required to confirm this (Schoop et al 2006b). Whilst various echinacea preparations appear useful in adults, clinical trials in childhood URTIs have produced disappointing results.

A 1999 review of 13 clinical trials consisting of 9 treatment studies and 4 prevention studies concluded that 8 of 9 treatment trials produced positive results, whereas 3 of four prevention trials suggested modest effects (Barrett et al 1999). In 2000, a Cochrane review was published that had assessed the evidence available from 16 clinical trials (8 treatment and 8 prevention) involving a total of 3396 subjects (Melchart et al 2000), and it concluded that some echinacea preparations may be better than placebo, with a majority of studies reporting favourable effects.

A more recent Cochrane systematic review (2006) evaluated data from 16 randomised, double-blind studies (Linde et al 2006), only five of which had been included in a previous Cochrane review. Whilst reviewers reported that evaluation was difficult because of the heterogeneity of preparations tested and variability of trial approaches, it was concluded that preparations based on the aerial parts of *E. purpurea* might be effective for the early treatment of colds in adults, although results are not completely consistent. Beneficial effects of other echinacea preparations and their use in prevention also exists but required further investigation. A 2006 meta-analysis by Schoop et al was more positive and concluded that the odds of experiencing a clinical cold were 55% higher with placebo than with pressed *Echinacea purpurea* juice or hydroethanolic *E. angustifolia* extract following inoculation with rhinovirus (Schoop et al 2006b). A 2007 meta-analysis published in *Lancet Infectious Diseases* was also positive and concluded that echinacea products from all species were beneficial in significantly decreasing the incidence (by 58%) and duration (by 1.4 days) of the common cold (Shah et al 2007b). Certain facets of quality of life improve with echinacea treatment during an URTI, according to a 2006 review, suggesting that treatment provides symptom relief and improved wellbeing (Gillespie & Coleman 2006).

Athletes

E. purpurea (Echinaforce Forte) was effective in the prophylaxis, as well as treatment, of the common cold in persons who actively participated in sport (Schoop et al 2006a). It is believed that echinacea attenuates mucosal immune suppression known to occur with intensive exercise and can reduce the duration of URTI that exercising people incur (Hall et al 2007).

There are many different confounding variables that make it difficult to definitively decide on the role of echinacea in the prevention and treatment of URTIs and, further, which echinacea preparations are best suited to the different uses. One key factor is the variability in chemical composition of echinacea test products and the lack of clear reporting by researchers about this factor. Additionally, there are methodological variations, different clinical settings, study populations and time of treatment initiation.

Future research should include a full disclosure of the chemical analysis of the echinacea preparation being tested so that systematic reviews will be able to use this information to separately assess the effects of each echinacea species, rather than combining them under the umbrella term of 'echinacea'. Moreover, larger prevention trials with appropriate outcome measures (e.g. the Wisconsin Upper respiratory Symptom Survey) should be conducted.

Paediatric studies

Four randomised studies published after 2000 were conducted with children and generally produced disappointing results (Cohen et al 2004, Spasov et al 2004, Taylor et al 2003, Weber et al 2005). A short review by Koenig and Roehr (2006) has also concluded that there is currently no evidence for the efficacy of *E. purpurea* in the treatment of URTI in children (Koenig & Roehr 2006). A 2008 clinical study with 60 children aged 12–60 months suggests that treating cold with *E. purpurea* in otitis-prone young children does not decrease the risk of acute otitis media, but is associated with a borderline

Clinical note — Common cold symptoms: What is usual?

The pathogenesis of the common cold involves a complex interplay between replicating viruses and the host's inflammatory response (Heikkinen & Jarvinen 2003). The onset of cold symptoms after viral incubation varies considerably and depends on the causative virus. In experimental rhinovirus infections, the onset of symptoms has been reported to occur as soon as 10–12 h after intranasal inoculation. Generally, the severity of the symptoms increases rapidly, peaks within 2–3 days after infection, and decreases soon after. The mean duration of the common cold is 7–10 days, but in a proportion of patients some symptoms can still be present after 3 weeks. Symptoms typically start with a sore throat, which is soon accompanied by nasal stuffiness and discharge, sneezing and cough. The soreness of the throat usually disappears quickly, whereas the initial watery rhinorrhoea becomes thicker and more purulent over time and can be accompanied by fever, most usually in children. Other symptoms associated with the cold syndrome include hoarseness, headache, malaise and lethargy.

increased risk of having at least one episode of acute otitis media during a 6-month follow-up compared to placebo (Wahl et al 2008).

Commission E approves the use of *E. purpurea* herb as an immune system support in cases of respiratory and lower urinary tract infection, and *E. pallida* root as supportive treatment in influenza-like infections (Blumenthal et al 2000).

Wound healing

Several uncontrolled clinical studies support the topical use of echinacea to enhance wound healing. A trial involving 4598 people investigated the effects of a preparation consisting of the juice of the aerial parts of *E. purpurea* on various wounds, burns, skin infections and inflammatory skin conditions (Kinkel et al 1984). Topical application of echinacea produced a 85% overall success rate, and the key constituent responsible for enhancing wound healing appears to be echinacoside (Speroni et al 2002).

Commission E approves the external use of *E. purpurea* herb for poorly healing wounds and chronic ulcerations (Blumenthal et al 2000).

Herpes infection

Based on the herb's antiviral activity against HSV-1 in vitro, it is also used in the treatment of herpes infections.

Genital herpes

A prospective, double-blind, placebo-controlled, crossover trial conducted over 1 year investigated the effects of an extract of the plant and root of *E. purpurea* (Echinaforce 800 mg twice daily) on the incidence and severity of genital herpes outbreaks in 50 patients (Vonau et al 2001). The study found no statistically significant benefit compared with placebo after 6 months of therapy.

Reducing chemotherapy side effects

Results from a small, open, prospective study of subjects with advanced gastric cancer suggest that intravenous administration of a polysaccharide fraction isolated from *E. purpurea* may be effective in reducing chemotherapy-induced leucopenia (Melchart et al 2002). Test subjects had advanced gastric cancer and were undergoing palliative chemotherapy with etoposide, leucovorin and 5-fluorouracil. The median number of leukocytes 14–16 days after chemotherapy was 3630/microlitre (range 1470–5770) in the patients receiving herbal treatment compared with 2370/microlitre (870–3950) in the patients of the historical control group ($P = 0.015$).

Radiation-associated leucopenia

Equivocal evidence exists for the use of echinacea in radiation-induced leucopenia, according to a small number of randomised studies (Ulbricht & Basch 2005). The product tested was Esberitox, which contains ethanolic extracts of three herbs, including root of echinacea.

Halitosis

A study with healthy volunteers suggests that a palatal adhesive tablet containing echinacea may serve as an effective means of treatment for patients complaining of oral malodour, because it resulted in a significant reduction in both oral malodour scores and volatile sulphide compound (VSC) levels. The reduction in VSC levels was significantly higher than with zinc and chlorhexidine (Sterer et al 2008).

Recurrent candidiasis

The herb is used to treat recurrent candidiasis, chiefly because of its antifungal and immunostimulant properties. Controlled studies are unavailable to determine effectiveness in this condition.

OTHER USES

Echinacea has also been used to treat UTI, allergies, acne and abscesses, and as adjunctive therapy in cancer (Mills & Bone 2000). It has also been used to prevent exercise-induced immunosuppression (Gleeson et al 2001). In practice, it is prescribed with other herbs to treat common infections and to prevent infections generally.

DOSAGE RANGE

General guide

- Dried herb: 3 g/day of either *E. angustifolia* or *E. purpurea*.
- Liquid extract (1:2): 3–6 mL/day of either *E. angustifolia* or *E. purpurea*. This dose may be increased to 10–20 mL/day in acute conditions. Treatment is usually started at the first sign of URTI and continued for 7–14 days.

Specific guide

- *E. angustifolia* dried root: 1–3 g/day.
- *E. purpurea* dried root: 1.5–4.5 g/day.

Clinical note — Safety of echinacea

The safety of echinacea has come into question in recent years due to two different articles that were poorly described in the press. One was a case report of suspected anaphylaxis reported in the *Medical Journal of Australia* (Mullins 1998). On closer inspection, the article describes an atopic woman who had taken nearly a dozen supplements at once, as well as double the recommended dose of a liquid echinacea product, before experiencing symptoms suggestive of anaphylaxis. Successful treatment consisted of oral promethazine and no other intervention. After the event, hypersensitivity was confirmed by skin prick and RAST testing, suggesting that an allergic response did occur.

In 2002, a second report described in detail five allergic reactions to different echinacea preparations and further stated that 51 adverse reactions involving echinacea had been reported to Adverse Drug Reactions Advisory Committee (ADRAC) (Mullins & Heddle 2002). Unfortunately, this time the media omitted the important fact that these cases were reported over a 21-year period. Once again, a closer look at the article finds approximately half of those reports were of suspected allergic responses and of those, only two could certainly be linked to echinacea use, with 10 classified as probable and 12 as possible. Considering an estimated 200 million doses of echinacea are used by Australians each year, the relative lack of adverse reports is impressive.

- *E. purpurea* dried aerial parts: 2.5–6.0 g/day.
- *E. purpurea* expressed juice of fresh plant: 6–9 mL/day.
- *E. pallida* ethanolic extract of root: 2–4 mL/day.

Although controversy still exists over which part of the plant and which particular plant has the strongest pharmacological activity, it appears that the cold-pressed juice and ethanolic extract of the aerial parts of *E. purpurea* and the hydroethanolic extracts from the roots of *E. angustifolia* are the most studied preparation for URTIs.

ADVERSE REACTIONS

Echinacea is well tolerated. Short-term use of echinacea is associated with a good safety profile, with a slight risk of transient, reversible and self-limiting gastrointestinal symptoms and rashes (Huntley et al 2005).

Overall, echinacea is safe for asthmatics and only in rare instances has been associated with allergic reactions or disease exacerbation (Huntley et al 2005).

It is unclear whether children are more prone to rashes with *E. purpurea* than adults. One study found that rash occurred in 7.1% of children using echinacea compared with 2.7% taking placebo (Taylor et al 2003), whereas a more recent study failed to identify allergic responses or adverse reactions in children with echinacea use (Saunders et al 2007).

There is no clear evidence from basic science or human studies to show that echinacea causes liver toxicity (Ulbricht & Basch 2005). Echinacea (8000 mg/day) taken over 28 days resulted in an increase in serum erythropoietin levels at days 7, 14 and 21, but did not significantly alter red blood cell, haemoglobin and haematocrit levels (Whitehead et al 2007). A single 350-mg dose of *E. purpurea* had no effect on electrocardiographic and blood pressure measurements (Shah et al 2007a).

One clinical study has reported that 1 g *E. purpurea* administered over 10 days altered the gastrointestinal microflora by significantly increasing total aerobic bacteria and bacteria belonging to the *Bacteroides* genus, but not significantly changing the number of enteric bacteria, enterococci, lactobacilli, bifidobacteria or total anaerobic bacteria (Hill et al 2006). Moreover, a review reported several ocular adverse effects due to *E. purpurea* (Santaella & Fraunfelder 2007). One case report exists where it is believed that an ethanolic extract of *E. pallida*, taken 10–20 days before, may have induced or exacerbated severe thrombotic thrombocytopenic purpura (TTP) in a healthy 32-year-old man (Liatsos et al 2006).

SIGNIFICANT INTERACTIONS

There are reports that urge to great caution when using echinacea with anticancer and antiretroviral agents (Meijerman et al 2006, van den Bout-van den Beukel et al 2006), due to possible effects on drug metabolising and transporting enzymes. However, most of the evidences are based on in vitro studies, of which some may not be of clinical relevance in vivo, but some should definitely be considered (Huntimer et al 2006). However, one recent review found only eight papers that contained primary data relating to drug interactions and concluded that there are no verifiable reports of herb–drug interactions with any echinacea product (Freeman & Spelman 2008).

CYP450 enzymes

Whilst in vitro studies have found evidence of weak inhibitory activity for *E. purpurea* on CYP1A2, CYP2D6, CYP2C19, CYP2D9 and CYP3A4 (Hansen & Nilsen 2008, Hellum et al 2007, Modarai et al 2007) further indicating that the alkylamide concentration was a chief determinant of activity on CYP 3A4 (Hansen & Nilsen 2008, Modarai et al 2007, Raner et al 2007); however, these findings have limited clinical relevance in vivo (Heinrich et al 2008). Two recent studies conducted with healthy volunteers showed again no effects on CYP2D6 (Gurley et al 2008, Hellum & Nilsen 2007). Previously, a study of healthy volunteers found that echinacea had no significant effect on CYP1A2, CYP2D6, CYP2E1 or CYP3A4 activity (Gurley et al 2004). In contrast, Gorski et al (2004) identified a complex effect on CYP3A4, which can be described as near self-cancelling inhibition of intestinal 3A4 with induction of hepatic CYP3A4 (Stargrove et al 2008). In other words, the net effect on availability of CYP3A4 substrates was essentially unchanged. This study used 400 mg of powdered dried root of *E. purpurea* taken four times daily for 8 days (Gorski et al 2004).

P-glycoprotein (P-gp)

Inconsistencies between in vitro and clinical results were also found among studies investigating effects on P-gp. In vitro tests revealed inhibition of P-gp for *E. purpurea* (Hansen & Nilsen 2009, Hellum & Nilsen 2008) which has been isolated to the *n*-hexane extracts (of all three echinacea species) and isolated polyacetylenes and polyenes from *E. pallida* (Romiti et al 2008). However, a clinical trial of 18 healthy volunteers failed to detect significant alteration to digoxin pharmacokinetics for *E. purpurea* indicating the effect on P-gp is not clinically significant (Hellum & Nilsen 2008).

Cyclophosphamide

Echinacea appears to increase the immunostimulatory effect of low-dose cyclophosphamide, which may be detrimental in autoimmune disease where low doses are used (Stargrove et al 2008) — the clinical significance of this observation is unknown — avoid until safety can be assured.

Immunosuppression agents (e.g. cyclosporin)

Theoretically, there may be an antagonistic pharmacodynamic interaction with immunosuppressive medication, but the clinical relevance is unclear. Exercise caution when using immunosuppressive agents and echinacea concurrently.

Myelosuppressive chemotherapeutic agents

Use of echinacea between treatment cycles may theoretically improve white cell counts, reduce dose-limiting toxicities on myelopoeisis and improve patient's quality of life — potentially beneficial interaction under professional supervision.

CONTRAINDICATIONS AND PRECAUTIONS

Contraindicated in people with allergies to the Asteraceae (Compositae) family of plants (e.g. chamomile, ragweed).

Commission E warns against using echinacea in cases of autoimmune disorders, such as multiple sclerosis, SLE and RA, as well as tuberculosis or leukocytosis (Blumenthal et al 2000) based on theoretical considerations and case reports with a questionable causal relationship; however, this warning does not appear to be warranted (Lee & Werth 2004). Boullata and Nace recommended the avoidance of echinacea use in patients with autoimmune disease (Boullata & Nace 2000), but this recommendation was only seen as the 'extrapolation from experimental observations of echinacea's effects on the immune system' by other authors (Logan & Ahmed 2003). Moreover, no adverse effects were reported when echinacea was consumed by mice afflicted with autoimmune (type 1) diabetes for up to 18 weeks. Instead, a consistent, long-lasting immunostimulation of only NK cells was observed, thus warranting further research (Delorme & Miller 2005). In addition, recent human studies reported safe and effective systemic echinacea treatment of low-grade autoimmune idiopathic uveitis resulting in longer steroid-free treatment periods for patients on echinacea treatment (Neri et al 2006).

In practice, echinacea has been successfully used by herbalists in autoimmune disease without mishap (Mills & Bone 2005).

Duration of use

Based on evidence that parenterally administered echinacea reversibly depresses immune parameters, Commission E has recommended that echinacea should not be used for more than 8 weeks. However, in a study in which it was taken orally for up to 6 months, no changes in immune parameters were detected (Vonau et al 2001). As such, no conclusive evidence demonstrates that long-term use is detrimental.

PREGNANCY USE

Oral use of echinacea has generally been considered safe in pregnancy when used in recommended doses (Mills & Bone 2005). This was substantiated by preliminary results from a prospective study of 206 women who had inadvertently taken echinacea during their pregnancy, which found that gestational use was not associated with an increased risk for major malformations (Gallo et al 2000). Moreover, a recent review concluded that echinacea is non-teratogenic when used during pregnancy, but that caution should prevail when using echinacea during lactation until further high-quality human studies can determine its safety (Perri et al 2006).

Studies in animal models have reported that echinacea preparations derived from *E. purpurea* produce unwanted effects in pregnant animals such as interference with embryonal angiogenesis (Barcz et al 2007), alteration of maternal haemopoiesis, fetal growth and a reduction in number of viable fetuses (Chow et al 2006). Due to the high rate of false positives obtained in such animal studies and problems with extrapolating data to humans from these models, the clinical significance of these findings remains unknown.

PRACTICE POINTS/PATIENT COUNSELLING

- Different types of echinacea have demonstrated immunomodulating, anti-inflammatory, antifungal, antiviral and antioxidant activity.
- Overall, clinical studies support the use of echinacea in URTIs, such as bacterial sinusitis, common cold, influenza-like viral infections and streptococcal throat. Current evidence is strongest for supporting its use as acute treatment in URTIs with some evidence supporting its use as prophylactic treatment.
- Several uncontrolled clinical studies support the topical use of echinacea to enhance wound healing.
- Echinacea is also used to treat UTI, allergies, acne and abscesses, as adjunctive therapy in cancer, herpes virus infections and candidiasis.
- Although controversy still exists over which part of the plant and which particular plant has the strongest pharmacological activity, it appears that the cold-pressed juice and ethanolic extracts of the *E. purpurea* plant and *E. angustifolia* root are the most studied preparations for URTIs.

PATIENTS' FAQs

What will this herb do for me?

Echinacea stimulates immune function and may also have antifungal, antiviral and anti-inflammatory activity. Scientific research generally supports its use as an acute treatment for URTIs in adults and possibly as prevention against URTIs. Applied to the skin, it may also enhance wound healing and be useful for chronic wounds. It also has anti-inflammatory actions.

When will it start to work?

As an acute treatment for URTI, echinacea should be started when the first signs and symptoms of infection appear.

Are there any safety issues?

Echinacea is well tolerated, although allergic reactions are possible in rare cases.

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Elder

HISTORICAL NOTE The elder tree has enjoyed much popularity throughout the ages. Ancient Egyptians used elderflowers to heal burns and improve their complexion. Throughout England elder was termed 'the medicine chest of the country people', and Native Americans used elder for coughs, colds, infections and skin conditions. Elderflowers are a favorite ingredient in herb teas, cordials and some wines.

COMMON NAME
Elder

OTHER NAMES
Black elder, common elder

BOTANICAL NAME/FAMILY
Sambucus nigra/*Caprifoliaceae*

PLANT PART USED
Flower or ripe berry

CHEMICAL COMPONENTS

Flowers
Flavonoids, primarily quercertin, isoquercertin, rutin and astragaline (Dawidowicz et al 2006, Wach et al 2007). Elderflowers also contain essential oils.

Berries
Anthocyanins are abundant in the berries, including cyanidin 3-sambubioside-5-glucoside, cyanidin 3,5-diglucoside, cyanidin 3-sambubioside, cyanidin

3-glucoside and cyanidin 3-rutinoside. Cyanidin 3-sambubioside is the most abundant anthrocyanin and accounts for more than 50% of all anthocyanins found in the berries (Veberic et al 2009, Murkovic et al 2000). The berries also contain flavonoids including quercertin, quercertin 3-rutinoside and quercetin 3-glucoside, organic acids and sugars (Veberic et al 2009). The unripe berries contain cyanogenic glycosides (Dellagreca et al 2003).

MAIN ACTIONS

There is very little research evaluating the actions of elderflower, even though it is the flowers that are most commonly used. Recently there has been increasing interest in the berries and therefore much of the research reviewed below has focused on these extracts.

Antioxidant

Elderflowers contain flavonoids such as quercertin, isoquercertin and rutin which all possess potent antioxidant properties (Dawidowicz et al 2006). The berries also contain these flavonoids and additionally have appreciable amounts of anthocyanins, chiefly cyanidin 3-sambubioside and cyanidin 3-glucoside (Veberic et al 2009, Murkovic et al 2000).

The effects of dietary cyanidin-3-O-glucoside (2 g/kg) and a concentrate of elderberry (2 g/kg) on the plasma and tissue concentrations of tocopherol and cholesterol were investigated for a period of 4 weeks in vivo (Frank et al 2002). Cyanidin-3-O-glucoside increased the levels of vitamin E in the liver and lungs and appeared to have a sparing effect. Cholesterol levels were not affected but both cyanidin-3-O-glucoside and elderberry reduced the amount of saturated fatty acid in the liver. Higher temperatures (100 degrees C) during aqueous extraction appear to yield a higher flavonoid content (Dawidowicz et al 2006).

Antiviral

In vitro studies have shown that Sambucol® (contains 1.9 g of elderberry extract per 5 mL, other ingredients include raspberry extract, sucrose, citric acid and honey) is effective against ten strains of influenza virus (Zakay-Rones et al 1995).

Immunostimulating

The standardised black elderberry product Sambucol® has been shown to increase the production of certain inflammatory cytokines (IL-1 beta, TNF-alpha, IL-6, IL-8) in human monocytes (Barak et al 2001). It is proposed that this may be one of the mechanisms via which elderberry improves immune system activity. Another study confirmed these results and in addition showed that elderberry also increases the anti-inflammatory cytokine IL-10 (Barak et al 2002). An in vitro study using a lectin isolated from elderflower (*Sambucus nigra* agglutinin) found the extract increased the release of IL-4 from basophils (Haas et al 1999).

Anti-inflammatory

An extract of elderflower was found to reduce inflammatory mediators in monocytes, macrophages and neutrophils incubated with whole cells of the periodontal pathogens *Porphyromonas gingivalis* and *Actinobacillus actinomycetemcomitans* (Harokopakis et al 2006). The extract appeared to inhibit the activation of nuclear factor kappa B and phosphatidylinositol 3-kinase. Controlled trials are needed, however these preliminary studies suggest that elderflower may be useful to attenuate the inflammation in periodontitis.

Diuretic

Elderflower has traditionally been used as a diuretic agent. An in vivo study found that the extract possessed diuretic properties comparable to the reference product hydrochlorothiazide (Beaux et al 1999). The extract also increased sodium excretion.

Antidiabetic

An aqueous extract of elderflowers has been shown to increase insulin secretion and enhance muscle glucose uptake (70%), glucose oxidation (50%) and glycogenesis (70%) in pancreatic beta cells in vitro (Gray et al 2000). The insulinotropic effects of elder were slightly stronger with a hot preparation. An aqueous extract of elder failed to increase glucose diffusion in another in vitro study (Gallagher et al 2003). The authors theorise that the anti-diabetic effects of elder may not be related to intestinal absorption.

OTHER ACTIONS

Elderflowers are also commonly used as diaphoretic agents to increase sweating during temperatures or fevers. It is believed that the action is greatly improved by the use of a hot infusion. They are also employed as expectorants and decongestants for the sinuses.

CLINICAL USE

Influenza

The elderberry extract Sambucol® (contains 1.9 g of elderberry extract per 5 mL, other ingredients include raspberry extract, sucrose, citric acid and honey) was evaluated in a multi-centre, randomised, placebo controlled clinical trial to investigate its efficacy in decreasing the severity and duration of influenza A and B infections (Zakay-Rones et al 2004). Sixty patients aged between 18 and 54 years were enrolled in the study when they had three or more symptoms of influenza (fever, malaise, nasal discharge etc). Patients were given 15 mL 4 times daily with meals for 4 days. The first dose was given within 48 hours of the onset of symptoms. The global evaluation scores for the elderberry group using visual analogue scales showed a significant improvement after an average of 3.1 days ($\pm$ 1.3) as compared to 7.1 ($\pm$ 2.5) days for the placebo group ($P < 0.001$).

The same extract was investigated in a previous study in 27 children and adults during an outbreak of influenza B Panama (Zakay-Rones et al 1995). Children were given 2 tablespoons of mixture for 3 days, whilst adults received 4 tablespoons for the same duration. Patients were followed for 6 days and their symptoms were monitored. A significant

improvement in symptoms was seen in 93.3% of the cases in the treatment group within 2 days as compared to 91.7% of the patients in the placebo group who were feeling better after 6 days ($P < 0.001$).

Cholesterol

A recent randomised, double-blind, placebo-controlled pilot study investigated the effect of elderberry juice on serum cholesterol and triglyceride levels (Murkovic et al 2004). Two studies were performed; in the first 34 healthy volunteers took capsules containing either spray-dried elderberry juice (400 mg containing 10% anthocyanes) or placebo three times a day for two weeks. A subgroup of 14 participants continued for another week to further evaluate the resistance of LDL-cholesterol to copper-induced oxidation. In the second study six subjects took a single dose of elderberry juice 50 mL together with a fat-laden breakfast to test the short-term effects of elderberry on serum lipid levels.

Results from the first study found that a small but not statistically significant change was noted in cholesterol concentrations in the elderberry group (from 199 to 190 mg/dL) compared to the placebo group (from 192 to 196 mg/dL). Additionally, elder didn't improve LDL-cholesterol oxidation within the three-week study period. Results from the second experiment also showed that elder failed to significantly reduce postprandial triglyceride concentrations after a high fat meal.

OTHER USES

Colds, fever, inflammation of the eyes, skin disorders, wounds, bronchitis, sinusitis, chronic nasal catarrh, hay fever, pleurisy, sore throat, measles and scarlet fever.

Commission E approves the use of elderflowers as a diaphoretic and to increase bronchial secretion (Blumenthal et al 1998).

DOSAGE RANGE

General guide

Flowers

- Tea: 10–15 g flowers/day.
- Liquid extract: 2–6 mL of 1:2 extract/day.

Berries

- Elderberry syrup: usually contains 30–38% elderberry; dose at 15 mL, 3 times daily (Sambucus nigra (elderberry) 2005).
- Powdered extracts: often available in 500 mg capsules, dose 2–3 times daily (Sambucus nigra (elderberry) 2005).

According to clinical studies

- Influenza: 15 mL of the syrup, 4 times daily.

ADVERSE REACTIONS

Elderberries have been generally well tolerated in clinical trials (Zakay-Rones et al 1995, 2004). Although there are no clinical studies using elderflowers, it is generally thought that they are most likely to also be very safe. In large doses elder may produce nausea, diarrhoea and polyuria (Mills & Bone 2005).

SIGNIFICANT INTERACTIONS

Controlled studies are not available. therefore interactions are based on evidence of activity and are largely theoretical and speculative.

Diuretic drugs

Elderflower appears to possess diuretic effects. Increased diuresis is possible with concomitant use — observe (Beaux et al 1999).

Hypoglycaemic drugs

Elderflower has demonstrated hypoglycaemic effects in vitro; the clinical significance of this observation remains unknown — observe (Gray et al 2000, Gallagher et al 2003).

CONTRAINDICATIONS AND PRECAUTIONS

A small number of people in the general population may experience allergy to elderflowers as shown by skin prick and RAST tests (Forster-Waldl et al 2003). Avoid in sensitive patients.

Never consume unripe or uncooked berries. They contain cyanogenic glycosides and can be dangerous.

PREGNANCY USE

Elder is likely to be safe when consumed in dietary amounts, however safety is not known when used in larger quantities.

PRACTICE POINTS/PATIENT COUNSELLING

- Elder is a popular herbal medicine and both the fruit and berry are used medicinally.
- Elderflower exhibits anti-inflammatory, antioxidant, diaphoretic, diuretic and anti-diabetic properties. The berry also possesses antioxidant properties and is also anti-viral.
- Commission E approves the use of elderflowers as a diaphoretic and to increase bronchial secretion.
- Elderflower has been used traditionally to treat colds, influenza, scarlet fever, bronchitis, sinusitis, hay fever and skin disorders.
- Clinical evidence supports the use of elderberry in influenza.
- The unripe and uncooked berries however should never be consumed as they contain cyanide.

PATIENTS' FAQs

What will this herb do for me?

Elder may be useful in the treatment of colds and flu, sinusitis and bronchitis. It may also be used to treat diabetes, however this use is less certain.

When will it start to work?

Clinical trials of elderberry in influenza have shown that on average the duration of illness was reduced from 6 days to 3 days, suggesting that elder works quite quickly. Elder, when taken as a hot infusion, appears to work immediately by increasing diaphoresis.

Are there any safety issues?
Elderflowers and berries appear to be very safe. The unripe and uncooked berries however should never be consumed as they contain cyanide.

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Eucalyptus

HISTORICAL NOTE Indigenous Australians traditionally used eucalyptus to treat fevers and respiratory infections, accounting for its name 'fevertree'. European settlers also recognised the medicinal qualities of eucalyptus and surgeon Considen is credited with producing the first essential oil sample in 1788. Bosisto investigated oils from several Australian plants and in 1854 eventually produced essential oils commercially in association with Müeller, a pharmacist. Bosisto and Müeller concentrated on oils rich in 1,8-cineole, which includes *Eucalyptus* species. In the late 1800s, articles about its medicinal use appeared in medical journals such as *The Lancet*, focusing on its potential in scarlet fever and diphtheria.

COMMON NAME
Eucalyptus

OTHER NAMES
Aetheroleum Eucalypti, cineole, *Oleum Eucalypti*, *Essence of eucalyptus rectifiee*

Common names include Australian fever tree leaf, blue gum, eucalyptol, fever tree, gum tree, red gum, stringy bark tree.

BOTANICAL NAME/FAMILY
Eucalyptus species (family Myrtaceae)

The species most commonly used in healthcare are:
- *Eucalyptus globulus* (blue gum)
- *Eucalyptus citriodora* (lemon scented gum)
- *Eucalyptus dives* (broad leaf peppermint)
- *Eucalyptus polybractea*.

There are more than 500 species of eucalyptus trees and shrubs native to Australia, but many species are cultivated in other parts of the world.

PLANT PARTS USED
The essential oil is extracted by steam distillation from fresh twigs and leaves. Modern eucalyptus essential oils are primarily extracted from *E. polybractea*, *E. dives*, *E. leucoxylon*, *E. sideroxylon*, and *E. radiata* in Australia, but other species are used in other countries (Lassak & McCarthy 2001).

CHEMICAL COMPONENTS
The major chemical constituents under the general heading 'eucalyptus' consist of oxides and hydroterpenes, primarily 1,8-cineole, which is the most significant constituent and ranges from 54–95% depending on the species. The 1,8-cineole component is particularly high in *E. globulus* and *E. radiata*. Eucalyptus also contains citronellal, camphone, fenchone, limonene, phellandrene and pinene depending on the species (Clarke 2002).

The exact chemical composition of an oil depends on the particular species from which it

is extracted. There are small amounts of alpha-pinene (2.6%), alpha-cymene (2.7%), aromadendrene, ciminaldehyde, globulol and pinocarveol and *d*-limonene, alpha-phellandrene, camphene and alpha-terpinene (Bisset 1994, Bruneton 1995, Serafino et al 2008).

Other essential oils high in 1,8-cineole include *Rosmarinus officinalis* ct. cineole, *Laurus nobilis, Cinnamomum camphora* ct. cineole and *Melaleuca cajuputi*.

MAIN ACTIONS

The main reported actions are expectorant, antitussive (Misawa & Kizawa 1990), nasal decongestant (Burrows 1983, FDA 1994), analgesic (Gobel 1995) and antispasmodic in animal and human studies. Antimicrobial and anti-inflammatory activity has also been reported in animal and human studies.

Antitussive

Antitussive effects were compared with codeine in guinea pigs in which cough was mechanically stimulated. Essential oil 5% in normal saline was administered by inhalation and had a significant antitussive effect relative to codeine ($P < 0.05$) (Misawa & Kizawa 1990). The antitussitive effects of 1,8-cineole were demonstrated in humans in 1980 in a single blind cross over study in healthy volunteers using a commercially available chest rub where eucalyptus was the active ingredient in the blend (Packman & London 1980). It appears that 1,8-cineole interacts with the M8 (TRPM8) receptor potential channel, the cool-sensitive thermoreceptor primarily affected by menthol, which produces a cooling sensation (Behrendt et al 2004). However, the antitussive effect may also be due to an effect on pulmonary C-fibres, which also contain TRPM 8 receptors.

Nasal decongestant

Two clinical studies have demonstrated that inhalation of eucalyptus oil reduces nasal congestion (Burrows 1983, FDA 1994). Likewise, Cohen & Dressler (1982) showed statistically significant differences in patients with acute coryza inhaling a volatile mixture of menthol 56% and eucalyptus oil 9% for 20 minutes compared to a control group on 14 of the 22 indices of respiratory function, measured from baseline to 60 minutes after inhalation. In contrast, Burrows et al (1983) showed no decongestant effect of inhaling camphor, eucalyptus or menthol for five-minute periods via a face mask ($n = 31$), although cold receptors in the nose were stimulated, creating a sensation of increased airflow and improved comfort.

Antimicrobial

Previous studies indicate eucalyptus has antimicrobial activity in vitro against *Pseudomonas aeruginosa*, *Bacillus subtilis*, *Enterococcus faecalis* and *Escherichia coli* (Kurrerath & Mundulaldo 1954), herpes simplex (Schnitzler et al 2001) and oral pathogens (Takarada et al 2004). A clinical observational study involving 30 patients with head and neck cancer and necrotic malodorous ulcers demonstrated improved quality of life and social interaction with the addition of a twice daily cleansing of the ulcers with an essential oil mix whose main component was eucalyptus (Warnke et al 2006). In addition, the researchers reported evidence of re-epithelialisation and anti-inflammatory effects.

Anti-inflammatory

Eucalyptus inhibits prostaglandin synthesis in vitro (Wagner 1986) at a concentration of 37 micromol/L. Anti-inflammatory and antinociceptive effects have been demonstrated in animal models (Ulbricht & Basch 2005). Alternatively, a study in which 1,8-cineole was injected into the rat hindpaw demonstrated that eucalyptus induced oedema, most likely due to the release of mast cell mediators (Santos & Rao 1997). The clinical implications of this finding for topically applied eucalyptus oil require further investigation. Anti-inflammatory activity of *E. radiata* has been demonstrated in patients with dry and weeping dermatitis, most probably due to inhibition of inflammatory markers such as TNF-alpha, COX enzymes, 5-lipoxygenase and other leukotrienes, and it could be an alternative to topical steroid medicines (Hadji-Minglou & Bolcato 2005, Santos & Raos 2000). Juergens et al (2003) demonstrated 1,8-cineole maintained lung function four times better than controls in a double blind clinical trial of patients ($n = 32$) with severe steroid-dependent bronchial asthma. Patients were randomly assigned to 1,8-cineole 200 mg 3 times daily for 3 weeks or placebo. Steroid doses were reduced by 2.5 mg every 3 weeks. Twelve of the 16 receiving 1,8-cineole remained stable despite reduced steroid doses.

Analgesic

Analgesic properties are attributed to the monoterpene components of eucalyptus oil. The monoterpenoid profile differs among eucalypt species and may account for variations in therapeutic effect. *E. globulus* has a high 1,8-cineole content (60–90%) (Juergens et al 1998). Silva et al (2003) investigated the analgesic and anti-inflammatory effects of *E. tereticornis, E. citriodora* and *E. globulus* in rats. The results showed central and peripheral analgesic effects of the three oils.

OTHER ACTIONS

Eucalyptus oil is metabolised in the liver; however, evidence is contradictory as to whether it induces the cytochrome P450 enzyme system. One study conducted with an animal model demonstrated a slight increase in CYP4A expression (Ngo et al 2003), whereas 1,8-cineole has demonstrated CYP450 induction in vitro and in animal studies (Ulbricht & Basch 2005). *E. globulus* induces a cell-mediated immune response, and morphological and functional activation in human macrophages stimulates the phagocytic response (Serafino et al 2008).

CLINICAL USE

Eucalyptus oil has been investigated in numerous forms; however, there is a lack of controlled, clinical studies.

Respiratory conditions

Eucalyptus oil is used as symptomatic treatment in obstructive respiratory conditions such as bronchitis, asthma, the common cold and other conditions associated with catarrh of the upper respiratory tract. Although it is used internally and externally in Europe for these indications, in Australia the oil is generally used externally in vaporisers, chest rubs and nasal inhalations.

Nasal decongestant properties were assessed in 31 healthy volunteers using inhalations of 10 mL of essential oil for 5 minutes. There was no effect on nasal resistance to air flow, but there was a stimulant effect on the cold receptors in the nose and the majority of subjects reported being able to breathe more easily (FDA 1994). A single-blind, parallel clinical trial (n = 234) was conducted to assess whether vaporised essential oil reduced nasal congestion compared with steam. The essential oil was significantly more effective ($P < 0.02$), but only in the first hour after inhalation. Other researchers found no significant differences in nasal decongestion compared with placebo (Burrows 1983). There was no significant difference between placebo and topically applied *E. piperita* to the forehead and temples to treat headache in a randomised, double crossover trial (n = 32); however, cognitive performance and muscle and mental relaxation were greater in the essential oil group (Gobel 1995).

Aromatherapy

Eucalyptus, as it is traditionally used in aromatherapy, has not been systematically investigated under clinical trial conditions. Therefore, most evidence is derived from traditional sources.

Aromatherapists use eucalyptus for its mentally uplifting and stimulating effects and to aid concentration. It is also used in massage and vaporisers to relieve respiratory symptoms, treat minor skin infections and acne, and relieve headache and muscular aches and pain. Usually eucalyptus oil is included in a blend of 3–5 essential oils for a massage but may be used alone for an inhalation.

One study investigating the effects of topical application of eucalyptus oil to the forehead and temples found it was an ineffective treatment for headache (Gobel 1995).

OTHER USES

Eucalyptus oil is often included in OTC and other medicines in various formulations such as rubs, mouthwashes, 'cold and 'flu' preparations, cleansing products, inhalers, soaps and insect repellents in which the 1,8-cineole content is standardised to 80–90%. Bosisto's Eucalyptus Oil is commonly sold in supermarkets and has an Aust R label (10908). It is not used in aromatherapy and is dispensed in a ribbed poison bottle with a childproof cap.

Dust mite removal

Eucalyptus oil can be formulated with a kitchen detergent concentrate to form an inexpensive acaricidal wash that reduces the number of live mites found in blankets during normal machine washing (Tovey & McDonald 1997). When compared with detergent concentrate alone, a 30-minute pre-wash soak of woollen blankets with the eucalyptus oil/detergent formula reduced the number of live mites that could be recovered by 97%. This eliminates the need for very hot water and may maintain low allergen levels in bedding for longer than normal laundering alone because mites are adversely affected by low concentrations of eucalyptus oil vapour, which lingers for 2–3 days. In this study, the dishwashing liquid detergent concentrate (Kit, L&K, Rexona, Sydney, Australia) was used to form an emulsion in water because the essential oil is not soluble in water.

Cleaning agent

Washing in diluted eucalyptus oil is also used as a method of removing stains from fabric; however, it does leave a faint characteristic odour for 2–3 days despite rinsing and drying, and some people may find this irritating.

Malodorous necrotic ulcers

These ulcers are a major concern for cancer patients and can lead to social isolation and reduced QOL because current treatments inadequately reduce the foul smell to acceptable levels. A paper published in 2006 reported that rinsing the ulcers twice a day with an antibacterial essential oil mixture (mainly eucalyptus oil) resulted in complete disappearance of odour by day 3 or 4 in all patients (n = 30) (Warnke et al 2006). The eucalyptus was used in combination with a standard course of antibiotics. A number of beneficial secondary findings were anti-inflammatory activity, promotion of healing and complete re-epithelialisation, and emotional relief on resolution of the condition.

DOSAGE RANGE

Dose recommendations vary, but generally low doses are used. Internal formulations may take longer to show an effect than conventional medicines.

- Inhalation: 12 drops in 150 mL of boiling water or 5 drops in a nebuliser, which delivers approximately 35 mg (unpubl. data: Harris & Harris – Aromatic Medicine: The Interfaces of Absorption, seminar course notes, Melbourne, 2003). High doses are not recommended because they can irritate the eyes and mucous membranes and may trigger an asthma-like attack.
- Mouth wash: 20 mL (0.91 mg/mL) solution gargled twice daily.
- Massage: traditionally aromatherapists use essential oils as 3.5–5% in a carrier substance but doses between 5 and 20% are used for adults and much lower doses for children and older people.
- Ointments, creams, gels and poultices: 5–10% in a carrier substance such as beeswax.
- Internal use: 0.3–0.6 mL/day essential oil 1–4 times daily; capsules 100–200 mg; lozenges 0.2–15.0 mg dissolved slowly in the mouth every 30–60 minutes.

Most Australian aromatherapists do not currently administer essential oils via the internal route (oral, vaginal and rectal), but they are administered via these routes in other countries, especially France.

TOXICITY

Toxicity symptoms occur rapidly, but may be delayed for hours and include altered conscious state, drowsiness and unconsciousness, which are dose-dependent. Symptoms reported in other studies include epigastric burning, nausea, vomiting, dizziness, muscular weakness, delirium and convulsions.

The acute oral LD_{50} dose of 1,8-cineole in rats is 2.48 g/kg and the dermal LD_{50} dose in rabbits is > 5 g/kg.

Fatal poisoning has occurred in children after accidental ingestion of whole or diluted eucalyptus oil in amounts ranging from 2 to 10 mL. Tibballs (1995) reported 109 children who were admitted to hospital for eucalyptus oil poisoning in an 11-year period; 27 had been accidentally poisoned when an adult administered the oil orally by mistake and most of the remaining 82 children had ingested the oil from a vaporiser. Another review of 41 cases of eucalyptus oil poisoning (Webb & Pitt 1993) indicated that 80% were asymptomatic. There was no relationship between the amount of oil ingested and the presence and severity of symptoms.

The Victorian Poisons Information Centre (see Appendix 3) recommends all patients who ingest ≥ 1 mL of eucalyptus oil be assessed in an emergency department. The centre attributes the toxicity to the cineole, terpene and phellandrene content and indicates that although hydrocyanic acid is only present in small amounts it may be responsible for most of the toxicity.

ADVERSE REACTIONS

Eucalyptus oil is generally safe when used externally in an appropriate manner.

A number of adverse reactions are reported for topical application, including systemic toxicity in a 6-year-old girl, and urticaria, contact dermatitis and skin irritation in other cases (Darben 1988). However, when considering the risks of topical application of eucalyptus oil the state of the skin must be considered as well as the individual's susceptibility to atopic conditions such as eczema and asthma.

Allergic reactions to lozenges have also been reported anecdotally.

Inhalations may irritate the eyes and mucous membranes.

SIGNIFICANT INTERACTIONS

Due to the lack of clinical evidence, interactions are theoretical and speculative.

CNS depressants

Oral ingestion of eucalyptus has been associated with CNS depression, therefore additive effects are theoretically possible — caution.

Drugs metabolised by CYP 450

Some evidence suggests CYP induction is possible; however, it is not known which CYP enzymes are affected, thus making recommendations difficult. Interactions are unlikely when used topically or inhaled, but could theoretically occur when used internally (Springhouse Corporation 2001).

PRACTICE POINTS/PATIENT COUNSELLING

- Eucalyptus essential oils are steam distilled from a number of *Eucalyptus* species, and have different chemical compositions depending on the species. Most contain a large proportion of 1,8-cineole, which appears to be responsible for the action on the respiratory system.
- Eucalyptus is primarily used in aromatherapy as an inhalation to relieve nasal congestion and in massage to relieve muscular aches and pain, as well as in ointments, gels and compresses, and via a vaporiser for mental stimulation and to aid concentration.
- It is used internally in lozenges, tinctures and conventional medicines.
- When used topically in an appropriate manner, eucalyptus oil is considered safe; however, several cautions exist to reduce the risk of adverse reactions and toxicity. People using eucalyptus essential oil should be monitored for allergies and it should not be applied to the face of children. Eucalyptus should not be used internally unless it is diluted and used in the recommended doses and dose intervals.
- Signs of poisoning usually occur rapidly and include confusion, irritability, respiratory distress, hypotension, nausea and vomiting. If poisoning is suspected medical care should be sought urgently. Do not induce vomiting. Use charcoal and monitor consciousness.
- Several drug interactions are theoretically possible; however, their clinical significance is unknown.

Hypoglycaemic agents

If used in combination with oral glucose-lowering conventional or complementary medicines it may contribute to hypoglycaemia (oral doses) — blood glucose levels should be monitored (Springhouse Corporation 2001).

CONTRAINDICATIONS AND PRECAUTIONS

Essential oils are not recommended in the first 3 months of life because the barrier function of the skin is not fully developed. In addition, inhaling menthol can induce transient apnoea in premature infants due to its effects on the TRPM 8 receptor (Javorka et al 1980); thus, essential oils containing 1,8-cineole should not be applied on or near the face of babies and small children. *E. globulus* may cause skin allergy in susceptible individuals (those prone to asthma and allergies, and with a previous reaction to eucalyptus).

Eucalyptus oil should not be administered internally to children or people with inflammatory gastrointestinal tract disease or impaired liver function, or during pregnancy.

Eucalyptus oil should not be applied to the face, especially of infants and young children because of the risk of bronchospasm and irritation.

The oil should be stored out of the reach of children and confused people.

Vaporisers containing eucalyptus essential oils should also be placed out of reach. Poisoning has occurred following ingestion from vaporisers.

Oily carrier fluids should not be used for nasal sprays because they inhibit protective nasal ciliary movements and could cause lipid pneumonia.

The essential oil is highly flammable and represents a fire risk when used in candle vaporisers.

PREGNANCY USE

No studies have been undertaken. The essential oil is not teratogenic in animal studies, but doses of 500 mg/kg cross the placenta in large enough amounts to stimulate hepatic activity in rodents (Jori & Briatico 1973). Aromatherapists do not use eucalyptus essential oil during pregnancy, especially in the first trimester.

PATIENTS' FAQs

What will this essential oil do for me?

Eucalyptus essential oil can be used in a vaporiser or on tissues to help clear the nose and make breathing easier in the presence of an URTI. It can also increase mental alertness. In a massage blend eucalyptus can help relieve muscular and arthritic pain.

Eucalyptus oil can be added to the washing machine to help kill dust mites in human clothes and animal bedding. Dust mites are responsible for many respiratory conditions, such as asthma.

When will it start to work?

Inhaled eucalyptus oil usually acts quickly and provides symptomatic relief quickly. Oral doses and massage blends usually take longer to have an effect.

Are there any safety issues?

Ingested eucalyptus oil has caused poisoning especially in children and therefore any source of the oil, including vaporisers, should be placed out of reach.

Eucalyptus can irritate the eyes and mucous membranes. It should be kept away from the face, especially of infants and children.

Ingested eucalyptus oil could affect the action of some medicines such as antidepressants, sedatives and anaesthetic agents. It increases absorption of nicotine.

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Evening primrose oil

OTHER NAMES
EPO, primrose oil, butter rose, cow slip, fever plant, huile d'onagre, king's cure all, mayflower, Our Lady's key, palsywort, sundrop.

BOTANICAL NAME/FAMILY
Oenothera biennis (family Onagraceae)

PLANT PART USED
Fixed oil from the seed. A suitable extract must be obtained from cold-pressing rather than heat extraction to avoid damaging the oil.

CHEMICAL COMPONENTS
Evening primrose oil contains essential fatty acids (EFAs). EFAs are polyunsaturated fatty acids containing two or more double bonds. EPO contains about 70% linoleic acid (LA) and 9% gamma-linolenic acid (GLA) (Horrobin 2000), as well as oleic, palmitic and stearic acids, campesterol and beta-sitosterol. Due to the position of its double bonds, EPO is classified as an omega-6 (n-6) fatty acid.

Borage seeds (18–26%) and blackcurrant oil (15–20%) also contain high amounts of GLA; however, research suggests that they are not necessarily any more potent on a gram-for-gram basis and it has been postulated that this is possibly due to other biologically active components of EPO or the minor stereodimensional differences in the GLA contained within the different oils (Fan & Chapkin 1992).

MAIN ACTIONS
The two main actions of EFAs are related to their roles in the structures of membranes and in the synthesis of a wide variety of derivatives that regulate numerous aspects of cellular activity. With regard to EPO, its main actions relate to its EFA content, GLA in particular.

Anti-inflammatory
Although GLA is a theoretical precursor for arachidonic acid (AA) and as such could also generate pro-inflammatory eicosanoids, such as the 2-series prostaglandins, 4-series leukotrienes and platelet-activating factor, the evidence to date suggests that GLA can encourage uptake of dihomo-GLA (DGLA) into cell membranes and this in turn inhibits the synthesis of AA metabolites. In addition to this, the direct metabolites of DGLA include prostaglandin E_1 (PGE_1), which has been shown to inhibit inflammation, regulate immunity, cause vasodilation and reduce blood pressure, improve flexibility of red blood cell membranes, induce insulin receptors and inhibit platelet aggregation and thrombosis (Horrobin 1990). Consequently, the net effect of this omega-6 oil is anti-inflammatory, which distinguishes it clearly from other non-GLA n-6 oils (Fan & Chapkin 1998).

GLA and DGLA have been shown to reduce inflammation and excessive immune reactivity in experimental models of arthritis, autoimmune disease, allergic and chronic inflammatory disorders (Godfrey et al 1986; Kunkel et al 1981a, 1981b, Mertin 1984, Tate et al 1988).

Dermatological effects
The anti-inflammatory effect of EPO has been most extensively studied in relation to skin disorders. In addition, n-6 fatty acids are involved in maintaining the integrity of the water impermeability barrier of the skin. Both LA and GLA, but not other EFAs, seem to be capable of this (Horrobin 1990).

Antithrombotic activity
GLA is metabolised to DGLA, which is a precursor to the 1-series of PGs. Increases in PGE_1 production result in a cascade of reactions that ultimately inhibit platelet aggregation and cause vasodilation. Additionally, red cell membranes deficient in EFAs become stiffer than normal, resulting in reduced capacity of red cells to flow through the capillaries and, therefore, adequately oxygenate target tissues (Horrobin 1990).

Other actions
Bone metabolism
Oral GLA and eicosapentaenoic acid (EPA) in the ratio 3:1 have been shown to significantly increase intestinal calcium absorption, calcium balance and bone calcium in rats, compared with controls that consumed LA (sunflower oil) and alpha-LA (linseed oil) (3:1) or a commercially available rat chow (Claassen et al 1995).

Hypotensive effects
Vegetable oils, including sunflower oil, linseed oil and EPO, have been shown to enhance the effects of several antihypertensive drugs, including dihydralazine, clonidine and captopril, in rats under experimental conditions (Hoffmann et al 1984).

A study examining the effects of salt-loading on blood pressure development in borderline hypertensive rats found that dietary sunflower and fish oils abolished the pressor response, reducing blood pressure below control levels (Mills et al 1989).

Antidiabetic effects
Several studies have indicated that treatment with EPO can prevent or reverse diabetic neuropathy in animals. The effect does not seem to be mediated neither by regulating the sorbitol or other polyol levels in peripheral nerves, nor by having any effect on the control of blood sugar. The interval between oral intake of EPO and its effect in peripheral nerves of rats was studied 35 days after induction of diabetes. EPO did not affect nerve conduction velocity in the first 12 h of its administration, but significantly increased it 24 h later. Nerve conduction needed 10 days to stabilise. The latency suggests that neuroactivity of EPO may be mediated by its metabolic products synthesised in the body, and not by constituents of the oil (Julu 1996). In another

experiment, diabetic rats not receiving EPO showed highly significant elevations of nerve sorbitol and fructose combined with a depletion of nerve myo-inositol. The rats had increased immunoreactivity and reduced nerve conductivity. Treatment of other diabetic rats with EPO attenuated conduction deficiency and in some cases completely prevented the development of the motor nerve conduction velocity deficit (Tomlinson et al 1989).

Alcohol metabolism

Many reports have now confirmed the teratogenic potential of alcohol in humans and in laboratory animals. A characteristic pattern of congenital anomalies is present in infants born to mothers with chronic alcoholism. Chronic consumption of ethanol causes a depletion of EFAs, partly by blocking GLA formation and partly by depleting DGLA. Treatment of pregnant rats with ethanol and EPO (Efamol), a rich source of GLA, led to a significant reduction in the embryopathic activity of ethanol (Varma & Persaud 1982).

Renal effects

Evening primrose oil, safflower oil and salmon oil have all shown a favourable effect on progression of renal failure in partially nephrectomised rats compared with controls that were fed beef tallow. The regulation of thrombotic and inflammatory mediators may explain the protective role of these oils (Barcelli et al 1986). Further studies showed that EPO and safflower oil may help to prevent diabetic nephropathy (Barcelli et al 1990). Compared with beef tallow, the oils appeared to have a clear beneficial effect on proteinuria, glomerular sclerosis and tubular abnormalities in diabetic rats. The effect was mediated via PG and thromboxane metabolism. No significant changes in plasma lipid composition were observed. Fish oils did not have an effect on renal disease, but decreased plasma lipids and inhibited eicosanoid synthesis by platelets and kidney cortex.

Diets containing fish oils, EPO or a combination all lowered plasma triglyceride and total cholesterol levels compared with diets containing beef tallow in experimentally induced nephritic syndrome in rats. However, only the combination of EPO and fish oil (75:25) affected HDL cholesterol levels. The combination prevented the 10-fold suppression of aortic 6-keto-PGF_{1alpha} caused by the fish oils. These changes in plasma lipids and eicosanoid production are potentially anti-atherogenic and may prevent glomerular sclerosis. The combination of EPO and fish oils may offer advantages over either family of fatty acids in nephrotic syndrome (Barcelli et al 1988).

Metabolites of EPA and GLA have been shown to slow or modulate the development of experimentally induced glomerulonephritis in rats (Papanikolaou 1987).

Antitumour effect

Excess dietary fat has been identified as a risk factor in the development of human breast carcinoma. However, the quality of fat may be more important than the overall quantity. Animals treated with EFAs from EPO and fish oils developed tumours that were significantly smaller than the two control groups treated with dietary olive oil or normal laboratory feed (Pritchard et al 1989).

CLINICAL USE

Although this review focuses primarily on GLA, evidence now suggests that n-6 fatty acid intake must be considered in relation to concurrent omega-3 (n-3) fatty acid intake to have a more consistent anti-inflammatory effect. As such, many studies are now using combination supplements or dietary changes that alter the ratio of n-3 to n-6 EFAs.

For more information about the n-3:n-6 fatty acid balance, which has implications in cardiovascular disease and cancer, refer to the monograph on Fish oils.

Deficiency

Like other essential nutrients, EFAs must be supplied by the diet; however, elucidation of a daily minimum requirement is not yet possible. Based on large dietary surveys and epidemiological evidence demonstrating a protective effect against cardiovascular disease incidence and mortality, a suggested dietary target for LA of 4–10% of total kJ intake has been set (NHMRC 2005). Besides insufficient intake, secondary deficiency states are also possible due to faulty EFA metabolism.

The first and rate-limiting step in EFA metabolism is the LA desaturation, requiring delta-6-desaturase amongst other enzymes. A deficiency or significant impairment of the desaturase enzyme, due to dietary or lifestyle factors, could lead to a deficiency of GLA. Excessive consumption of LA could also lead to a relative deficiency of GLA. Direct supplementation with GLA may be clinically beneficial in both scenarios (Horrobin 1990).

It is now suspected that a number of common conditions, such as dermatitis, may be aggravated by, or in part caused by, an imbalance between n-3 and n-6 EFAs and a relative GLA deficiency.

Dermatitis and psoriasis

Research from the 1930s to the 1950s established that an n-6 EFA deficiency leads to inflammatory skin conditions in both animals and humans. While there is no deficit of LA in atopic eczema, with concentrations of LA tending to be elevated in blood, milk and adipose tissue of patients with atopic eczema, concentrations of its metabolites are substantially reduced. This suggests reduced conversion of LA to GLA (i.e. delta-6-desaturase impairment). In most studies, but not all, GLA administration has been found to improve general skin health: the clinically assessed skin condition, the objectively assessed skin roughness and the elevated blood catecholamine concentrations of atopic eczema. Together with ongoing research suggesting that atopic eczema may be a minor inherited abnormality of EFA metabolism in some cases (Businco et al 1993, Horrobin 2000, Kitz et al 2006, van Gool et al 2003), interventional studies using EPO or other

GLA rich oils have curiously failed to demonstrate efficacy on the whole.

Clinical studies

Earlier promising results, including a 1989 meta-analysis (Morse et al 1989), have been overshadowed by recent predominantly negative findings.

Evening primrose or borage oil, either alone or in combination with fish oils, in the most recent studies was found to be ineffective for atopic dermatitis in adults (Berth-Jones & Graham-Brown 1993, Henz et al 1999, Takwale et al 2003) and children (Takwale et al 2003) and adult psoriasis (Oliwiecki & Burton 1994). A study supplementing newborns considered high risk for atopy with GLA (≈40 mg/day), either directly through formula or via the mother, for up to 6 months, failed to reduce atopic dermatitis incidence; however, treatment lowered IgE levels for the first year of life (Kitz et al 2006).

In 2000, a substantial review was conducted by the National Health Service (NHS) Health Technology Assessment Programmes, looking at more than 15 studies involving either EPO or borage oil in the treatment of atopic dermatitis, and it was concluded that the largest and best-reported studies showed no convincing effect (Hoare et al 2000). A 2004 meta-analysis of EPO studies in atopic dermatitis concurred with these findings (van Gool et al 2004).

In spite of much negative evidence, occasional positive findings continue to surface. One such result published in 2008 comes from a study of Indian children with atopic dermatitis, administered EPO (500 mg to 5 g dependent upon age) for 5 months. A response rate of 96% was achieved in the EPO group compared with 32% for placebo and EPO was concluded to be an effective treatment.

Finally, both oral and topical EPO applications have been investigated in the uraemic pruritis experienced by hemodialysis patients with some success; however, more research is warranted to confirm efficacy for this specific presentation (Chen et al 2006, Yoshimoto-Furuie et al 1999).

Clinical note — Company interest bias in the evidence?

The research into the efficacy of EPO has attracted much criticism from different members of the scientific community. In particular, attention has been paid to the contrast between early 'strikingly' positive findings and the negative conclusions currently being drawn as a result of more in-depth analysis regarding the efficacy of EPO in the treatment of some conditions. While some may argue these results are due to improvement in research methodology, one editorial published in 2003 in the *British Medical Journal* implies that research funding from the manufacturers, selective inclusion of positive only studies in previous reviews and meta-analyses as well as partial suppression of negative findings has had a part to play (Williams 2003).

Female reproductive system disorders

Without doubt, the most popular use for EPO supplements relates to conditions of the female reproductive system. On the whole, the evidence, however, has been plagued by small and poorly designed studies (Stonemetz 2008).

Premenstrual syndrome

Interest in EPO supplements as a potential treatment for Pre Menstrual Syndrome (PMS) began in the early 1980s, largely as a result of investigational work published by David Horrobin, of three double-blind placebo-controlled studies and two open trials in women with premenstrual syndrome (Horrobin 1983).

Shortly afterwards, results from a study conducted by Brush et al provided a rationale for considering EPO supplementation for PMS. This study found that phospholipids' LA levels in women with PMS were significantly above normal, yet the concentrations of all metabolites were significantly reduced (Brush et al 1984). Based on these findings, researchers suggested that some women with PMS may not be able to adequately convert LA to GLA and as a result, sensitivity to luteal phase prolactin and steroids may be increased. As such, supplementation directly with GLA would bypass the problem and potentially normalise sensitivity and result in reduced symptoms.

For a time, these results stood unquestioned, until in 1990 another double-blind placebo-controlled trial involving 38 women failed to show evidence of efficacy over six cycles (Khoo et al 1990).

A comprehensive review published in 1996 identified seven placebo-controlled trials, although in two the randomisation was unclear. The two most well-controlled studies failed to detect a benefit for EPO supplements; however, as they were small, modest benefits cannot be excluded (Budeiri et al 1996). Interestingly, in one of these studies, the only significant benefit noted by the subjects was a mild reduction in breast pain.

Mastalgia

In spite of the earlier promising findings (Gateley et al 1992a, 1992b), a more recent 6-month, randomised, double-blind trial did not find that EPO, EPA or a combination of the two were significantly better than placebo in reducing the symptoms of mastalgia. Corn oil and corn oil with wheat germ oil were used as control oils. The decrease in days with pain was 12.3% for EPO and 13.8% for its control oil; the decrease in days with pain was 15.5% for fish oil and 10.6% for its control oil (Blommers et al 2002). A recent meta-analysis concurs with these findings, suggesting that EPO is no more effective than placebo in the treatment of mastalgia (Srivastava et al 2007); however, there has been ongoing speculation regarding the possible effects of the 'control oils' used in these trials (Stonemetz 2008).

Evening primrose oil has also been assessed for its ability in preventing fibro-adenomas. A small study of 21 patients found that EPO had no significant influence over the natural history of breast fibroadenomas (Kollias et al 2000). A more recent study

has also yielded negative results when compared with topical Non Steroidal Anti Inflammatory Drugs (NSAIDs), with significantly reduced efficacy, more reported adverse effects and ratings of less acceptability by the patients (Qureshi & Sultan 2005).

Dysmenorrhoea

Similar to the original findings of impaired omega-6 metabolism in PMS sufferers, recent research in dysemenorrhoeic women has revealed poor conversion of LA into DGLA, predisposing individuals to a pro-inflammatory state (Wu et al 2008). The study, which compared the effects of borage, sunflower and fish oil over 3 months, produced increased DGLA:AA in healthy women taking borage oil but not in dysmenorrheoic women. While this trial did not investigate clinical outcomes such as pain relief, EPO supplementation does not appear promising.

Endometriosis

A combination of GLA and EPA is better than placebo in relieving the symptoms of endometriosis according to one placebo-controlled study. Of those in the treatment group, 90% reported relief of symptoms compared with 10% of those in the placebo group (Horrobin 1990).

Oedema and hypertension during pregnancy

In a partially double-blind, placebo-controlled clinical trial, a combination of EPO, fish oil and magnesium oxide was found to be superior to placebo in lowering the incidence of oedema ($P = 0.004$) in pregnant women. Significantly, fewer women developed hypertension in the group receiving the oils and magnesium oxide. The three cases of eclampsia all occurred in the control group (D'Almeida et al 1992).

Menopausal hot flushes

According to one randomised, double-blind placebo-controlled study, EPO supplementation significantly reduces the maximum number of nighttime flushes, although other symptoms failed to respond. The study used a dose of four capsules daily (each containing 500 mg EPO and 10 mg vitamin E) over 6 months (Chenoy et al 1994).

A position statement of the North American Menopause Society (2004) concluded that evidence was lacking to warrant the use of EPO in the treatment of vasomotor symptoms of menopause.

Pregnancy

EFA supplementation during pregnancy has tended to focus on the omega-3s; however, several investigations of maternal docosahexaenoic acid (DHA) supplementation revealed a corresponding negative effect on plasma arachidonic acid (AA) levels of mothers (Geppert et al 2008). AA, like the omega-3s, is essential for fetal brain development and function; hence questions have been raised regarding possible ramifications of such an effect. Additionally, epidemiological research suggests that low intrauterine levels of (D)GLA may be linked to an increased risk of obesity, insulin resistance and hyperlipidaemia in later life. To address this issue, a placebo-controlled study was undertaken, administering 3.4 g of an EPO and fish oil blend (456 mg DHA, 73 mg EPA, 14 mg AA, 353 mg GLA) over 8 weeks in a group of 40 women. The co-administration of GLA at this dose appeared to counter the previously observed negative effect on plasma AA and researchers are proposing further trials to assess cognitive and other outcomes in offspring of mothers following such a protocol (Geppert et al 2008).

Another small study, published only as a conference abstract, investigated the effects of EPO 1 g three times daily in pregnant women over 1 week close to term (Ty-Torredes 2006), reporting a significant reduction in cervical length in the treatment versus placebo group and improved Bishop score. EPO is proposed as a potential cervical priming agent to enhance the success of vaginal delivery; however, no background theory to explain this hypothesis is provided.

Diabetes

The activity of delta-6-desaturase enzyme is compromised in patients with type 1 and type 2 diabetes mellitus, which can decrease the production of PGE_1, therefore possibly contributing to an overall inflammatory excess in these conditions, as demonstrated by increased levels of PGE_2 (Halat & Dennehey 2003).

The first randomised, double-blind placebo-controlled study investigating EPO as a treatment agent in type 1 and type 2 diabetes mellitus involved 22 patients with mild distal diabetic neuropathy. Patients were administered 360 mg/day of GLA or placebo for 6 months. Patients receiving GLA had statistically significant improvements in all measures of nerve function, wrist and ankle heat threshold values, as well as overall symptom scores. As there was no change in HbA_{1c} in the patients receiving EPO, improvements in symptoms were deemed to be independent of any effect on glucose control.

A subsequent larger, randomised, double-blind placebo-controlled study involved 111 patients with type 1 or 2 diabetes and mild or moderate neuropathy. Patients received either placebo or 480 mg/day of GLA for 1 year. At 1 year, patients who received GLA had a statistically significant increase in 13 of 16 neural function measurements compared with placebo, including a variety of motor conductivity, action potential and sensory tests. Greater benefits were observed in those patients who had glycohaemoglobin values less than 10% at baseline (Jamal & Carmichael 1990).

Currently, there is a need for more conclusive research; however, the evidence to date appears promising for EPO supplementation in mild to moderate neuropathy, even as an adjunct to conventional treatments.

Rheumatoid arthritis (RA)

EPO supplementation increases DGLA, a competitive inhibitor of pro-inflammatory PGs and leukotrienes, and therefore reduces the inflammatory response (Belch & Hill 2000). As such, EPO supplements have been investigated in the management of RA, producing mixed results (Belch et al 1988,

Brzeski et al 1991, Hansen et al 1983, Jantti et al 1989, Veale et al 1994, Zurier et al 1996).

In one study, 16 patients with RA were given 540 mg GLA/day (EPO), 15 patients 240 mg EPA and 450 mg GLA/day (EPO/fish oil) and 18 patients an inert oil (placebo). The initial 12-month treatment period was followed by 3 months' placebo for all groups. Results at 12 months showed a significant subjective improvement for EPO and EPO/fish oil compared with placebo. Additionally, within 12 months, the patients receiving EPO and EPO/fish oil had significantly reduced their NSAID intake. After 3 months' placebo, those receiving active treatment had relapsed. Despite the decrease in NSAIDs, measures of disease activity did not worsen. It is suggested that EPO and EPO/fish oil produce a subjective improvement and allow some patients to reduce or stop treatment with NSAIDs. There is, however, no evidence that they act as disease-modifying agents (Belch et al 1988).

In a randomised, single-blind placebo-controlled trial (Zurier et al 1996), treatment with 2.8 g/day GLA resulted in a significant and clinically relevant reduction in RA symptoms and signs of disease activity. GLA therapy demonstrated a significant improvement in swollen joint count and score, tender joint count and score, duration of morning stiffness, patient's global assessment, patient's assessment of pain and degree of disability compared with baseline (measured by Health Assessment Questionnaire score). Not all of these parameters were significantly improved compared with placebo, but this may be due to the choice of safflower oil as a placebo. Olive oil, which contains oleic acid, also found in safflower oil, has been reported in other studies to benefit patients with RA (Brzeski et al 1991).

In one group of patients who were treated with GLA for 12 months, 16 of 21 showed meaningful improvement and 7 patients were able to decrease their NSAID and/or prednisolone dosage. GLA does not have a disease-modifying effect and supplementation must be long term. After 3 months without GLA supplementation, most patients experienced an exacerbation of symptoms. GLA was well tolerated during the trial with only three minor adverse reactions reported. Complete blood count and platelet count did not show abnormal results (Zurier et al 1996).

More recently, a 2004 systematic review of complementary medicine treatments for arthritis included 11 trials of GLA rich oils in RA (Soeken 2004). It was concluded that there was strong evidence that GLA supplementation significantly reduces the pain associated with this condition.

Cardiovascular diseases

There has been little clinical investigation of EPO in cardiovascular diseases, however when taken together with ongoing animal research, there is some evidence of cardiovascular actions.

Hypertension

A double-blind placebo-controlled study with a crossover design found that the combination of EPO and fish oils significantly lowered blood pressure in 25 non-obese black patients with mild–moderate uncomplicated essential hypertension after 8–12 weeks compared with placebo (sunflower and linseed oil) (Venter et al 1988). Other smaller studies have found a similar beneficial effect in hypertensive patients. A combination of 4 g GLA and DHA daily for 6 weeks reduced blood pressure in nine mildly hypertensive patients compared with placebo (sunflower oil) (Deferne & Leeds 1992).

EPO (1.3 g/day) significantly lowered blood pressure in mildly hypertensive but otherwise healthy subjects in a small placebo-controlled, double-blind short-term trial. EPO treatment led to a group reduction of systolic pressure (8.98 mmHg) and diastolic pressure (12.25 mmHg). The authors suggest that the effect may be mediated via GLA's effects on PG metabolism (Leeds et al 1990).

A study conducted in 2001 in mice demonstrated that consumption of a GLA-based diet significantly reduced aortic vessel wall medial layer thickness and reduced atherosclerotic lesion size. These results were reported by the researchers to indicate that dietary GLA can suppress smooth muscle cell proliferation in vivo and potentially retard the development of atherosclerotic plaques. Human trials are now required to confirm this effect (Fan et al 2001).

Lipids

Several animal studies using EPO have demonstrated lipid-lowering effects (Dasgupta & Bhattacharyya 2007, Fukushima et al 1997, Fukushima et al 2001), most consistently reducing triglycerides while increasing HDL concentrations, with few yielding negative results (Ford et al 2001). A small study comparing the effect of 30 g olive oil or 3 g EPO/day over 2 weeks produced similar results in 24 patients with coronary artery disease (Stolyhwo Gofron et al 2006). Interestingly, both statin and fibrate classes of lipid-lowering drugs affect physiological GLA concentrations in contrasting ways, with statins lowering phospholipid and cholesterol ester concentrations; fibrates increasing GLA triglyceride levels. The significance of these actions upon net lipid-lowering effects is yet to be determined (Nyalala et al 2008).

Other

Animal research has demonstrated GLA as being protective against ventricular fibrillation (Charnock 2000) while a human trial of EPO compared to five other oils taken over 8 months failed to improve endothelial function (Khan et al 2003). Recently, a new hypothesis of impaired desaturation of both omega-6 and -3 fatty acids as a potential initiator and perpetuator of atherosclerosis has also been postulated (Das 2007).

OTHER USES

Alcoholism

Essential fatty acids are major structural components of the brain and through their effects on membrane properties are essential for the proper

actions of neurotransmitters and nerve conduction. Ethanol has three main known actions on EFA and PG metabolism: it reduces blood LA levels and induces or exaggerates EFA deficiency states; it blocks metabolism of LA to EFA metabolites, which are known to be important in brain structure; and it enhances the conversion of DGLA to PGE_1 (Horrobin 1987).

Small clinical studies have found EPO somewhat beneficial in the treatment of alcoholism. In a double-blind placebo-controlled clinical trial, EPO significantly reduced the severity of the withdrawal syndrome and improved liver function during the early weeks of withdrawal from alcohol. Relapse rates over 6 and 12 months did not improve, but in those who did not relapse certain parameters of cerebral function improved significantly (Horrobin 1990).

Migraine

Gamma-linolenic acid may be beneficial in the prevention of migraine headache when used in combination with other nutritional supplements and as part of an overall management plan, according to an open, prospective, uncontrolled trial involving 168 migraine patients. In the study, patients took a combination of GLA and alpha-LA (1800 mg/day), other vitamins, coenzymes and antioxidants, and were instructed to lower their arachidonic acid intake. They were also instructed on correct techniques of self-medication and in stress-reduction and progressive relaxation techniques. Of the 129 patients who were evaluated after 6 months, 86% reported an improvement, with 22% of the total being free from migraine, while 14% were not able to implement the self-management of progressive relaxation and stress-reduction techniques. Severity and frequency of attacks were decreased in patients reporting a positive response. Significant reduction in nausea and vomiting was reported in all groups except the failure group (Wagner & Nootbaar-Wagner 1997). Although encouraging, further research using GLA as a stand-alone treatment is required to determine its role in achieving these impressive results.

Schizophrenia

A 2000 review of clinical trials concluded that although EPA (from fish oils) may help up to one-third of people avoid initiation of standard treatment with antipsychotic drugs, there is no clear evidence of any benefit from EPO (Halat & Dennehey 2003, Joy et al 2000). Some authors in fact suggest that EPO is not recommended in this population although there is conflicting evidence regarding this (Stonemetz 2008).

Raynaud's syndrome

Prostaglandin E_1 and prostacyclin have been used in Raynaud's syndrome, but as these compounds are unstable and require intravenous administration, other treatments that increase the body's own production of these chemicals have been sought, for example, by administration of the precursor EFA. A small, double-blind placebo-controlled study of 21 patients with Raynaud's phenomenon found that EPO significantly reduced the number of attacks as the weather worsened compared with placebo. Visual analogue scales assessing the severity of attacks and coldness of hands improved in the EPO group, but no changes were seen in either group for objective measures of blood flow although changes in platelet behaviour and blood prostanoids were observed (Belch et al 1985).

DOSAGE RANGE

- Like other essential nutrients, EFAs must be supplied by the diet. Unlike other essential nutrients, it has not yet been possible to identify a minimum daily requirement.
- To reduce the risk of rancidity, EPO is mostly administered in sealed soft gel capsules that are taken orally and should be cold-pressed form of the oil.

According to clinical studies

- Diabetic neuropathy 360–480 mg GLA, which is approximately four to six 1 g capsules per day (Halat & Dennehy 2003).
- Alcoholism, cardiovascular and inflammatory disorders: 0.5–2.8 g GLA/day (approximately 5.0–28.0 g EPO/day) (Belch & Hill 2000, Leeds et al 1990, Zurier et al 1996).
- EPO may be applied topically in the treatment of skin disorders.

ADVERSE REACTIONS

Mild gastrointestinal symptoms, such as nausea, flatulence, loose bowels and bloating have been reported (Bamford et al 1985, Stonemetz 2008). High doses of 5–10 mL/kg/day administered in animal models failed to detect toxic effects or carcinogenicity (Everett et al 1988).

SIGNIFICANT INTERACTIONS

Phenothiazines

Several case reports suggest that EPO may reduce seizure threshold and reduce drug effectiveness in patients with schizophrenia treated with phenothiazines (Vaddadi 1981, Stonemetz 2008). Avoid concomitant use.

Oral anticoagulants

Due to the antithrombotic effect of EPO, concomitant use may theoretically increase the risk of bleeding — use caution and monitor bleeding time and signs and symptoms of excessive bleeding (Stonemetz 2008).

Antiplatelet drugs

Concomitant use may theoretically increase risk of bleeding, but enhanced anti-inflammatory effects may also develop, making this a useful combination — observe patients taking this combination.

CONTRAINDICATIONS AND PRECAUTIONS

There is mixed evidence for EPO lowering the seizure threshold in people with epilepsy (Spinella 2001). Until safety can be better established, EPO should be used with caution by people with a history of partial complex seizure disorders such as

temporal lobe epilepsy. Schizophrenics treated with neuroleptic drugs (phenothiazines) should also use this supplement with caution as it may lower seizure threshold. Suspend use of high doses 1 week before major surgery (Stonemetz 2008).

PREGNANCY USE

Safety has not yet been firmly established in pregnancy, although studies with experimental models suggest it is safe (Stonemetz 2008). Furthermore, EPO combined with fish oils has been used successfully to reduce the incidence of pre-eclampsia (D'Almeida et al 1992). According to a small study investigating the effects of EPO in pregnant women close to term, EPO has potential as a cervical priming agent (Ty-Torredes 2006).

PRACTICE POINTS/PATIENT COUNSELLING

- Evening primrose oil contains a number of EFAs, most notably GLA, which is thought to be the most important for exerting pharmacological activity.
- It is suspected that GLA supplementation results in increased production of useful metabolites such as PGE_1, which inhibits inflammation, regulates immunity, causes vasodilation and reduces blood pressure, improves flexibility of red blood cell membranes, induces insulin receptors and inhibits platelet aggregation and thrombosis.
- Evening primrose oil appears beneficial in the treatment of diabetic neuropathy, RA and elevated triglycerides.
- In many disorders, EPO is combined with fish oils (EPA) for best results.

PATIENTS' FAQs

What is EPO?

Evening primrose oil is the oil from the seed of the plant known as evening primrose. A similar oil is made from borage seeds. The oil contains high amounts of GLA, which is the main active compound.

What will this supplement do for me?

Current evidence supports the use of EPO in the treatment of diabetic neuropathy, RA and cardiovascular disease.

When will it start to work?

Beneficial effects have been reported in some studies within 2–4 weeks' continuous use. However, long-term use is necessary for chronic diseases such as RA.

Are there any safety issues?

Evening primrose oil is generally well tolerated. Only minor gastrointestinal upset may occur. Should this happen, it is recommended the capsules be taken with meals. EPO should be avoided by some people taking anti-epileptic medicines and blood thinning medicines.

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Fenugreek

HISTORICAL NOTE Fenugreek's seeds and leaves are used not only as food, but also as an ingredient in traditional medicine. It is indigenous to Western Asia and Southern Europe, but is now mainly cultivated in India, Pakistan, France, Argentina and North African countries. In ancient times, it was used as an aphrodisiac by the Egyptians and, together with honey, for the treatment of rickets, diabetes, dyspepsia, rheumatism, anaemia and constipation. It has also been described in early Greek and Latin pharmacopoeias for hyperglycaemia and was used by Yemenite Jews for type 2 diabetes (Yeh et al 2003). In India, China and the Middle East, it is still widely used as a therapeutic agent. In the United States, it has been used since the 19th century for postmenopausal vaginal dryness and dysmenorrhoea (Ulbricht & Basch 2005).

COMMON NAME
Fenugreek

OTHER NAMES
Trigonella seeds, bird's foot, Greek hay, hu lu ba, methi, trigonella

BOTANICAL NAME/FAMILY
Trigonella foenum-graecum (family Leguminosae)

PLANT PARTS USED
Dried mature seed, although leaves are used less commonly.

CHEMICAL COMPONENTS
The main chemical constituents are fibre, tannic acid, fixed and volatile oils and a bitter extractive, steroidal saponins, flavonoids, polysaccharides, alkaloids, trigonelline, trigocoumarin, trigomethyl coumarin, mucilage (up to 30%), seven essential amino acids and vitamins A, C, D, B1, B2 and B3 (Bin-Hafeez et al 2003, Fisher & Painter 1996, Shang et al 1998, Zia et al 2001).

MAIN ACTIONS

Hypoglycaemic
The hypoglycaemic effect of fenugreek seeds has been demonstrated in numerous studies involving experimentally induced diabetes (both type 1 and type 2) in rats, dogs, mice, rabbits as well as diabetic humans (Alarcon-Aguilara et al 1998, Eidi et al 2007, Mohammad et al 2006, Madar et al 1988, Raju et al 2001, Ribes et al 1984, 1986, Riyad et al 1988, Sharma et al 1990, Vats et al 2002), and the effect has been described as slow but sustained (Puri et al 2002). Interestingly, no reduction of fasting or postprandial blood sugar levels was observed in a placebo-controlled study in non-diabetic people who used a dose of 5 g/day over 3 months (Bordia et al 1997).

The mechanism for the hypoglycaemic effect of fenugreek has been explored in many in vivo trials. The viscous fibre, galactomannan, reduces intestinal absorption of glucose and thus postprandial blood glucose (Srichamroen et al 2009). Fenugreek also has an insulinomimetic effect and may increase the sensitivity of tissues to available insulin (Puri et al 2002) and enhance utilisation of glucose (Al Habori et al 2001).

Anti-ulcerogenic activity
Both an aqueous extract and a gel fraction isolated from the seeds demonstrated significant ulcer-protective effects in vivo (Pandian et al 2002). The seed fractions given orally to test animals provided dose-dependent gastric protection against the effects of ethanol, which was as potent as that of omeprazole. Furthermore, histological studies found that the soluble gel fraction was significantly more protective than omeprazole. Preliminary research suggests that the polysaccharide composition and/or flavonoid components of the gel are responsible for the gastroprotective and antisecretory activities of the seeds.

Hypocholesterolaemic effect
Significant cholesterol-lowering activity has been demonstrated in several animal studies and human studies with diabetic volunteers (Boban et al 2008, Gupta et al 2001, Petit et al 1995, Rao et al 1996, Stark & Madar 1993, Sharma et al 1990, Sowmya & Rajyalakshmi 1999). Although the mechanism of action is still unclear, it appears that the fibre and steroidal saponins interact with bile salts in the digestive tract (Stark & Madar 1993). In one study, an unusual amino acid, 4-hydroxyisoleucine 5, was isolated and tested in dyslipidaemic hamsters and was found to significantly decrease plasma triglyceride levels by 33%, total cholesterol by 22% and free fatty acids by 14%, accompanied by an increase in HDL cholesterol:total cholesterol ratio by 39% (Narender et al 2006).

Immunostimulant activity

Enhanced humoral immunity, significant increases in macrophage activity and a stimulatory effect on lymphoproliferation have been demonstrated in vivo (Bin-Hafeez et al 2003). Stimulatory effects were observed at 100 mg/kg and in some cases at 250 mg/kg.

Anti-inflammatory and antipyretic activity

Potent anti-inflammatory activity was demonstrated in an animal model for both single-dose and chronic-dose applications of a dried leaf decoction of fenugreek (Ahmadiani et al 2001). The effectiveness of the 1000 mg/kg dose of the extract was relatively equal to 300 mg/kg sodium salicylate for single dosing; however, chronic administration was more effective than sodium salicylate. Additionally, the fenugreek decoction exhibited stronger antipyretic activity than that of sodium salicylate. These findings have been supported in a recent in vivo trial of a water-soluble fraction of fenugreek seed that was shown to have significant analgesic and anti-inflammatory actions (Vyas et al 2008).

Antinociceptive effects

Two studies in animal models have identified antinociceptive activity for fenugreek (Ahmadiani et al 2001, Javan et al 1997). This seems to be mediated through central and peripheral mechanisms. According to Javan et al (1997), the antinociceptive effects of 2000 mg/kg of the extract were more potent than those of 300 mg/kg sodium salicylate.

Effect on thyroid hormones

Administration of fenugreek seed extract for 15 days to both mice and rats significantly decreased serum liothyronine (T_3), suggesting that thyroxine (T_4)-to-T_3 conversion is inhibited and leads to increases in T_4 levels (Panda et al 1999).

Stimulates digestion

Traditionally, fenugreek is used to improve digestion. In vivo studies have identified that it enhances the activities of pancreatic and intestinal lipases, and sucrase and maltase, thereby providing support to this traditional use (Platel & Srinivasan 1996, 2000).

OTHER ACTIONS

Positive findings for other properties of fenugreek have been found in vitro and in vivo, including antioxidant, antihypertensive, hepatoprotective and chemoprotective actions (Annida & Stanely Mainzen Prince 2005, Amin et al 2005, Balaraman et al 2006, Bhatia et al 2006, Dixit et al 2005, 2008). The polyphenolic compounds of fenugreek seeds confer antioxidant and hepatoprotective properties comparable to silymarin in trials on rats (Kaviarasan & Anuradha 2007, Kaviarasan et al 2004, 2006, 2008). Antineoplastic activity has been observed for fenugreek in the Ehrlich ascites carcinoma model in mice (Sur et al 2001). Protodioscin, purified from fenugreek, has also exhibited antineoplastic activity on human leukaemia cell lines in vitro (Hibasami et al 2003). Fenugreek extract induces apoptosis in vitro to breast, pancreatic and prostate cancer cell lines, but not normal cells (Sebastian & Thampan 2007, Shabbeer et al 2009). Ethanol extract (50%) seemed to possess profound antiplasmodial activity in vitro (Palaniswamy et al 2008), but no in vivo trials have yet been undertaken. Although fenugreek contains coumarin constituents, a placebo-controlled study found that it does not affect platelet aggregation, fibrinolytic activity or fibrinogen (Bordia et al 1997). Traditionally, it is thought to promote lactation in nursing mothers and act as a general tonic.

CLINICAL USE

Dyspepsia and loss of appetite

Although controlled studies are unavailable, the increased activities of pancreatic and intestinal lipases seen in animal studies provide a theoretical basis for its use in dyspepsia.

Commission E approved the internal use of fenugreek seed for loss of appetite (Blumenthal et al 2000).

Elevated lipid levels

Several clinical studies conducted in people with and without diabetes have identified significant lipid-lowering activity with different fenugreek preparations, such as defatted fenugreek, germinated seed and hydro-alcoholic extracts (Bordia et al 1997, Gupta et al 2001, Sharma et al 1990, Sowmya & Rajyalakshmi 1999). As can be expected, the dose used and type of preparation tested have an influence over results.

An open study using a daily dose of 18 g germinated fenugreek seed in healthy volunteers demonstrated significant reductions in total cholesterol and LDL cholesterol levels. A placebo-controlled study found no effect after 3 months with a lower dose of 5 g seed daily (Bordia et al 1997, Sowmya & Rajyalakshmi 1999), suggesting that higher intakes may be required for lipid-lowering activity to become significant.

Diabetes

Fenugreek is a popular natural treatment used to aid blood sugar regulation in diabetes. In recent years, many in vitro and in vivo studies have been conducted in different models providing support for its use in diabetes; however, there have been relatively few human trials. Overall, clinical studies have produced positive results; however, interpretation is difficult because trials have used diverse preparations, various dosage regimens and outcome measures.

In one open study involving 60 people with type 2 diabetes, 25 g fenugreek seed powder taken together with lunch and dinner for 24 weeks produced significant reductions to fasting blood sugar levels and symptoms of diabetes, and improved glucose tolerance (Sharma et al 1996). A shorter 10-day randomised study of people with type 1 diabetes found that defatted fenugreek seed powder (50 g twice daily) significantly reduced fasting blood sugar level and improved glucose tolerance (Sharma

et al 1990). A double-blind, placebo-controlled study involving 25 volunteers with mild to moderate type 2 diabetes showed that 1 g/day hydroalcoholic extract of fenugreek seeds for 2 months improved insulin resistance and increased insulin sensitivity but had no effect on fasting blood glucose level at this low dose (Gupta et al 2001).

More recently, the efficacy and safety of fenugreek in the treatment of patients with type 2 diabetes mellitus were investigated in 69 patients whose blood glucose levels were not well controlled by oral sulfonylureas. This 12-week trial demonstrated that combined treatment of fenugreek with sulfonylureas improved glycaemic control, further reduced blood glucose levels and ameliorated clinical symptoms in the treatment of type 2 diabetes (Lu et al 2008). Fenugreek treatment was also found to be safe.

Lipid lowering in diabetes

Studies investigating the effects of fenugreek seed and seed powder have demonstrated significant lipid-lowering activity in this population. Oral doses of 25 g fenugreek seed powder taken twice daily significantly reduced serum total cholesterol, triacylglyceride and LDL cholesterol in hypercholesteraemia according to a study of hypercholesterolaemic type 2 diabetic patients. Results were taken at 3 weeks and 6 weeks (Moosa et al 2006). A placebo-controlled study using a lower dose of 2.5 g unaltered fenugreek seed twice daily over 3 months found that this was ineffective in type 1 diabetes but did have a lipid-lowering effect in patients with diabetes and coronary artery disease (Bordia et al 1997). In this population, total cholesterol and triglyceride levels were significantly reduced.

Studies with defatted fenugreek seed (100 g/day) in patients with type 1 diabetes also identified significant reductions in total cholesterol, LDL and VLDL cholesterol and triglyceride levels but no changes to HDL cholesterol under randomised conditions (Sharma et al 1990).

Ethanolic extracts of fenugreek have also demonstrated good results. A 2001 double-blind, placebo-controlled study found that a dose of 1 g ethanolic extract of fenugreek was able to significantly decrease serum triglyceride levels and increase HDL cholesterol in mild-to-moderate type 2 diabetes mellitus (Gupta et al 2001). Previously, similar results were obtained with an ethanolic extract of defatted fenugreek seeds in vivo, which produced an 18–26% reduction in plasma cholesterol level (Stark & Madar 1993).

In combination

A combination powdered mixture of three traditional Indian medicinal plants — fenugreek seeds, bitter gourd and jamun seeds — in raw and cooked form produced benefits in a study of 60 non-insulin-dependent people with diabetes. Daily supplementation of 1 g of this mixture for a 1.5-month period and then a further increase to 2 g for another 1.5 months significantly reduced the fasting and postprandial glucose levels in this population. A significant decrease in oral hypoglycaemic drug requirements was observed and for some subjects, cessation of drug therapy could be achieved after the 3-month feeding trial (Kochhar & Nagi 2005).

Promoting lactation

Although fenugreek has been used traditionally for centuries to increase milk production and improve lactation, no controlled studies are available to confirm effectiveness.

Externally — to reduce local inflammation

Although controlled studies are not available, evidence of anti-inflammatory and antinociceptive activity provides a theoretical basis for this indication.

Commission E approves the external use of fenugreek as a poultice for local inflammation (Blumenthal et al 2000).

OTHER USES

In Ayurvedic and Unani systems of medicine, fenugreek is used for treating fever, epilepsy, paralysis, gout, dropsy, chronic cough and piles. In Morocco, fenugreek is used as a preventive treatment against the development of kidney stones. There are some tests in experimental models, which provide some support for this use (Laroubi et al 2007).

The seeds are reported to have nutritive properties and to stimulate digestive processes, and have been used to treat a range of gastrointestinal disorders in the Indian system of medicine. It is also used as a general tonic, mixed with milk and sugar, to promote lactation and to lower lipid and glucose levels.

DOSAGE RANGE

Internal use

According to clinical studies

- General dose range: liquid extract (1:2): 2–6 mL/day.
- Diabetes: 50–100 g seed daily taken in divided doses with meals, or 1 g/day ethanolic seed extract.
- Lipid-lowering activity: according to the above studies, 18.0 g germinated fenugreek or 100 g defatted seeds daily taken in divided doses with meals.

External use

- As a poultice: 50 g powdered seed in 0.5–1 L hot water applied topically to affected area.

TOXICITY

Safety studies indicate that fenugreek is extremely safe. When consumed as 20% of the diet, it did not produce toxic effects in animal tests.

ADVERSE REACTIONS

One clinical study found that a dose of 50 g taken twice daily produced mild gastrointestinal symptoms, such as diarrhoea and flatulence, which subsided after 3–4 days. Allergic reactions have been reported, more usually a consequence of

cross-reactivity in patients with peanut allergy. Primary fenugreek allergy is rare (Faeste et al 2009). Rats fed a diet of 30% fenugreek seeds exhibited antifertility effects to the point of toxicity (Kassem et al 2006). Proportional doses in humans would be near impossible to administer.

SIGNIFICANT INTERACTIONS

Where controlled studies are not available, interactions are speculative and based on evidence of pharmacological activity and case reports.

Hypoglycaemic agents

Additive effects are theoretically possible in diabetes and drug dose reductions may be required in some patients — monitor serum glucose levels closely — potentially beneficial interaction.

Iron

Frequent use of fenugreek can inhibit iron absorption — separate doses by 2 hours.

Warfarin

Although there is a theoretical concern that concomitant use could increase bleeding risk due to the herb's coumarin content, this is unlikely. A placebo-controlled study found that fenugreek does not affect platelet aggregation, fibrinolytic activity or fibrinogen (Bordia et al 1997).

CONTRAINDICATIONS AND PRECAUTIONS

Fenugreek is contraindicated in people with allergy to the herb, which has been observed in several case reports (Patil et al 1997), or those with allergy to chickpeas, because of possible cross-reactivity (Ulbricht & Basch 2005). Monitor patients with thyrotoxicosis when using this herb at doses above usual dietary intake.

PREGNANCY USE

When taken in usual dietary amounts, fenugreek is likely to be safe; however, the safety of larger doses has not been scientifically evaluated.

PRACTICE POINTS/PATIENT COUNSELLING

- Fenugreek's seeds and leaves are used not only as food but also as an ingredient in traditional medicine systems.
- Clinical studies have identified significant hypoglycaemic and lipid-lowering activity; however, dosage forms and treatment regimens varied.
- In animal studies, fenugreek has been shown to exert immunostimulant, anti-inflammatory and antinociceptive activity, stimulate digestive enzyme production and provide significant antiulcerogenic effects.
- In practice, it is used to manage blood sugar levels in patients with diabetes, to lower cholesterol levels, to provide symptom relief in dyspepsia and to promote lactation.
- Externally it is made into a poultice with hot water and used as an anti-inflammatory application.

PATIENTS' FAQs

What will this herb do for me?

Fenugreek can lower blood sugar levels in patients with diabetes, reduce cholesterol levels and stimulate digestion. It may also protect the gastrointestinal tract from ulcers, stimulate immune function and provide anti-inflammatory and antipyretic effects. Traditionally, it has also been used to promote lactation.

When will it start to work?

Studies suggest that blood sugar effects can be seen within 10 days in type 1 diabetes, whereas lipid-lowering effects can take up to 3 months to establish. Traditionally, digestive effects are thought to occur soon after ingestion of the seeds.

Are there any safety issues?

Used as a food, fenugreek appears extremely safe but may interact with blood-thinning medicines. When used in high doses as a medicine, it may cause flatulence, diarrhoea and mild stomach discomfort. Allergies to fenugreek are possible. When used with diabetic medicine, it may increase sugar-lowering activity and safety should be monitored.

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Feverfew

HISTORICAL NOTE Feverfew has been used for centuries in Europe to treat headaches, arthritis and fever and used as an emmenagogue and anthelmintic agent. In the 1970s, it was 'rediscovered' by the medical establishment and subjected to clinical studies, which produced encouraging results that suggested feverfew was an effective prophylactic medicine for migraine headache.

OTHER NAMES
Altamisa, bachelor's button, camomile grande, featherfew, featherfoil, chrysanthemum parthenium, mutterkraut, matrem, tanaceti parthenii herba/folium

BOTANICAL NAME/FAMILY
Tanacetum parthenium (family [Asteraceae] Compositae)

PLANT PART USED
Leaf

CHEMICAL COMPONENTS
The leaves and flowering tops contain many monoterpenes and sesquiterpenes as well as sesquiterpene lactones (chrysanthemolide, chrysanthemonin, 10-epi-canin, magnoliolide and parthenolide), reynosin, santamarin, tanaparthins and other compounds. Until recently, the sesquiterpene lactone parthenolide was thought to be the major biologically active constituent. However, in vitro and in vivo research suggests that others are also present (Brown et al 1997, Pugh & Sambo 1988).

MAIN ACTIONS

Anti-inflammatory and analgesic
Several in vivo studies have identified anti-inflammatory and antinociceptive activity for feverfew extracts and parthenolide. When feverfew extracts were orally administered, or pure parthenolide was injected IP, significant dose-dependent, anti-inflammatory and antinociceptive effects were observed in animal models (Jain & Kulkarni 1999). Similarly, when feverfew extracts and parthenolide from *Tanacetum vulgare* was administered orally in a rat model, gastric ulcer index was significantly reduced (Tournier et al 1999).

The mechanisms responsible for these effects are not well elucidated. Jain and Kulkarni (1999) demonstrated that the antinociceptive effect was not mediated through the opiate pathway and was not associated with sedation. With regard to the anti-inflammatory effect, several mechanisms appear to be responsible.

Clinical note — Natural variations in parthenolide content
The amount of parthenolide present in commercial preparations of feverfew leaves varies significantly, with some exhibiting levels as high as 1.7% dry weight and others as low as 0.01% to non-detectable (Cutlan et al 2000). The study by Cutlan et al measured the parthenolide content in plants produced from seeds taken from over 30 different sources and germinated under identical conditions. According to this study, feverfew collected from the wild and distributed by botanical gardens or US Department of Agriculture seed banks yielded plants with the highest mean parthenolide value, and plants with yellow leaves also had significantly higher parthenolide levels than those with green leaves.

Two in vitro studies have found evidence of COX and lipoxygenase inhibition (Capasso 1986, Pugh & Sambo 1988), while other tests reveal no effect on COX (Collier et al 1980, Makheja & Bailey 1982). Inhibition of phospholipase A_2 has also been suggested (Heptinstall 1988). Direct binding and inhibition of I-kappa B kinase beta, an important subunit involved in cytokine-mediated signalling, has been demonstrated for parthenolide in test tube studies (Kwok et al 2001). Parthenolide also inhibits NO production, an important regulator and inducer of various inflammatory states (Wong & Menendez 1999). More recently, results from an in vivo study confirm that parthenolide inhibits proinflammatory cytokine responses, although the authors propose that proinflammatory mediators, including chemokines (MIP-2), plasma enzyme mediators (complement, kinin and clotting systems) and lipid mediators (COX, PG, platelet-activating factor) are also likely to be involved (Smolinski & Pestka 2003).

The essential oil constituent of feverfew, chrysanthenyl acetate, inhibits PG synthetase in vitro and also seems to possess analgesic properties (Pugh & Sambo 1988).

Antispasmodic
The results from several in vitro studies generally indicate that feverfew decreases vascular smooth muscle spasm (Barsby et al 1992, 1993a, 1993b, Collier et al 1980).

Inhibits serotonin release and binding
Parthenolide and several other sesquiterpene lactone constituents inhibit serotonin release but do not bind to $5HT_1$ receptors, according to in vivo data (Groenewegen & Heptinstall 1990, Marles et al 1992, Weber et al 1997a). Some tests with $5HT_{2A}$ receptors show parthenolide is a low-affinity antagonist (Weber et al 1997b), whereas other tests found no effect on $5HT_{2A}$ or $5HT_{2B}$ receptors. Feverfew extract potently and directly blocked $5HT_{2A}$ and $5HT_{2B}$ receptors and neuronally released 5HT, suggesting that feverfew powder or extracts are more effective than isolated parthenolide (Mittra et al 2000).

Anticancer activity
In the last five years, there has been increasing investigation into the parthenolide constituent from feverfew as an anticancer agent. It displays multiple mechanisms, which make it an attractive candidate for further cancer research.

Parthenolide has been shown to withdraw cells from cell cycle or to promote cell differentiation, and finally to induce programmed cell death (Pajak et al 2008). It has an ability to induce apoptosis in a variety of cancer lines, has chemosensitising properties and is non-toxic to normal cells. The potent anticancer activity of parthenolide is in part due to its ability to inhibit transcription factor NF-kappaB, thereby reducing survival potential in a number of cancer cells (Anderson & Bejcek 2008, Pajak et al 2008, Zunino et al 2007). The effect is specific to tumour cells. Parthenolide-induced generation of

reactive oxygen species (ROS) in cancer cells has also been shown to play a role in promoting apoptotic cell death. Interestingly, experiments in animal models indicate that in non-cancerous cells, parthenolide acts as an antioxidant molecule by increasing levels of intracellular glutathione resulting in a decrease in ROS. In contrast, an increase in ROS generation in response to parthenolide appears to increase apoptotic cell death in cancer cells.

Parthenolide is cytotoxic to several breast cancer cell lines such as one human cervical cancer cell line (SiHa), prostate tumour-initiating cells isolated from prostate cancer cell lines as well as primary prostate tumour-initiating cells, glioblastoma cells, pre-B acute lymphoblastic leukaemia (ALL) lines (Anderson & Bejcek 2008, Kawasaki et al 2009, Wu et al 2006, Zunino et al 2007).

A comparison of parthenolide treatment with that of the standard chemotherapy drug cytosine arabinoside (Ara-C) found it was much more specific to leukaemia cells (Guzman et al 2005), whereas Ara-C killed both leukaemia cells and normal cells to an equivalent extent; parthenolide showed significantly less toxicity to normal haematopoietic cells from bone marrow and cord blood.

An in vitro and in vivo study of parthenolide in breast cancer found that parthenolide has significant in vivo chemosensitising properties in the metastatic breast cancer setting (Sweeney et al 2005). Parthenolide was effective either alone or in combination with docetaxel in reducing colony formation, inducing apoptosis and reducing the expression of prometastatic genes *IL-8* and the antiapoptotic gene *GADD45beta1* in vitro. In an adjuvant setting, animals treated with parthenolide and docetaxel combination showed significantly enhanced survival compared with untreated animals or animals treated with either drug. The enhanced survival in the combination arm was associated with reduced lung metastases. In addition, nuclear NF-kappaB levels were lower in residual tumours and lung metastasis of animals treated with parthenolide, docetaxel or both.

Studies have now begun with a series of amino-parthenolide analogues, which have been synthesised by a conjugate addition of several primary and secondary amines to the alpha-methylene-gamma-butyrolactone function of the sesquiterpene lactone, parthenolide (Nasim & Crooks 2008).

OTHER ACTIONS

Inhibits platelet aggregation

Evidence is contradictory as to whether feverfew inhibits platelet aggregation. Several test tube studies and animal models have observed inhibition of platelet aggregation (Heptinstall et al 1988, Jain & Kulkarni 1999, Makheja & Bailey 1982). However, no significant effects were seen in a clinical study of 10 patients receiving feverfew (Biggs et al 1982).

Mast cell stabilisation

Tests with rat mast cells indicate that feverfew extract inhibits histamine release, but the mechanism of action is different from cromoglycate and quercetin (Hayes & Foreman 1987). Recent in vivo tests confirm that parthenolide significantly inhibits IgE-antigen-induced mast cell degranulation in a dose-dependent manner (Miyata et al 2008). The formation of microtubules is well known to be crucial for IgE-antigen-induced degranulation in mast cells, and parthenolide exhibits tubulin/microtubule-interfering activity. The mast cell stabilisation effect is rapid in vivo as an immediate-type allergic response was induced in test animals and strongly inhibited by parthenolide administration.

CLINICAL USE

Prophylaxis of migraine headache

Traditionally, feverfew has been used in the treatment and prevention of headaches. Its growing popularity in the UK, in the 1970s and 80s, prompted researchers to investigate its usefulness under controlled trial conditions. The first double-blind study investigating feverfew in migraine prophylaxis was published in 1985 and involved 17 patients who had been chewing fresh feverfew leaves on a daily basis (Johnson et al 1985). Therapeutic effect was maintained when capsules containing freeze-dried feverfew powder were continued, whereas those allocated placebo capsules experienced a significant increase in the frequency and severity of headache, nausea and vomiting during the early months of withdrawal.

Clinical note — Migraine

Migraine is a common episodic familial headache disorder characterised by a combination of headache and neurological, gastrointestinal and autonomic symptoms. It has a 1-year prevalence of approximately 18% in women, 6% in men and 4% in children before puberty (Silberstein 2004). Several underlying mechanisms are considered responsible for the onset of migraine.

One of the genes linked to migraine is associated with dysfunction in P-type neuronal calcium channels, which mediate 5-HT and excitatory neurotransmitter release. This dysfunction can impair release of 5-HT and predispose patients to migraine attacks or impair their self-aborting mechanism (Silberstein 2004). Additionally, NO may be involved in the initiation and maintenance of migraine headache (Ferrari 1998). Migraine aura is now thought to be caused by neuronal dysfunction, not ischaemia, and headache begins while cortical blood flow is reduced.

In clinical practice, the three goals of migraine-preventive therapy are to reduce attack frequency, severity and duration, improve responsiveness to treatment of acute attacks, and improve function and reduce disability. Ultimately, choice of treatment should be based on efficacy, adverse effects and co-existing conditions with a full therapeutic trial taking 2–6 months.

Since then, numerous clinical studies have been conducted to determine the role of feverfew in the prevention of migraine headache.

In 2000, Ernst and Pittler published a systematic review of six randomised, placebo-controlled, double-blind trials of feverfew as a prophylactic treatment and concluded that the current evidence favours feverfew as an effective preventative treatment against migraine headache, and is generally well tolerated.

A more recent Cochrane systematic review of five placebo-controlled, randomised, double-blind trials (n = 343) concluded that there was insufficient evidence to determine whether feverfew was superior to placebo in reducing migraine frequency or incidence, severity of nausea or severity of migraines (Pittler & Ernst 2004). A closer look at the studies reveals that results were mixed, methodological quality varied and various dosage regimens, administration forms and extracts were used. One study used three different dosing regimens for a CO_2 extract, two studies used an alcoholic and CO_2 extract, three studies used dried feverfew leaves for 8–24 weeks and one study used an alcoholic extract for 8 weeks. Interpretation of test results is made even more difficult when one considers the naturally occurring chemical variations among the preparations.

The authors have offered several explanations for the inconsistent clinical findings and point out that previous negative studies used extracts standardised for parthenolide concentration; however, it is possible that other compounds found in whole-leaf preparations may also be important for pharmacological activity. In vivo studies support this view (Mittra et al 2000). Additionally, the negative results obtained by some studies may be due to underdosing.

Since then, positive results were obtained for a CO_2 extract of feverfew in a randomised, double-blind, placebo-controlled, multicentre study of 170 patients (Diener et al 2005). Active treatment with feverfew (MIG-99) at a dose of 6.25 mg, three times daily, significantly reduced the frequency of migraine headache episodes over a 16-week period.

In combination

A number of trials have tested feverfew in combination with other herbs and nutritional supplements. Shrivastava et al (2006) tested a combination of willow bark (600 mg/day) and feverfew (600 mg/day) known as Mig-RL in a 12-week prospective study for the prophylaxis of migraine and shown to significantly reduce attack frequency and severity. The combination was selected because previous in vitro studies identified that feverfew and willow bark inhibit binding to 5-HT(2A/2C) receptors and the combination of willow bark with feverfew further inhibited 5-HT(1D) receptors, whereas feverfew on its own did not. Combination herbal treatment significantly reduced migraine attack frequency by 57.2% at 6 weeks ($P < 0.029$) and by 61.7% at 12 weeks ($P < 0.025$) in nine of 10 patients, with 70% of patients having a reduction of at least 50%. Attack intensity was reduced by 38.7% at 6 weeks ($P < 0.005$) and by 62.6% at 12 weeks ($P < 0.004$) in ten of ten patients, with 70% of patients having a reduction of at least 50%. Attack duration decreased by 67.2% at 6 weeks ($P < 0.001$) and by 76.2% at 12 weeks ($P < 0.001$) in ten of ten patients. Two patients were excluded for reasons unrelated to treatment. Self-assessed general health, physical performance, memory and anxiety also improved by the end of the study. The treatment was well tolerated and no adverse events occurred (Shrivastava et al 2006).

The combination of feverfew with ginger (GelStat Migraine) in a sublingually administered fluid was evaluated as an acute treatment in an open-label study involving 29 patients with 1-year history of migraine meeting International Headache Society (IHS) diagnostic criteria with or without aura, 2–8 migraines per month and ≤15 headache days per month. People ingested the test substance during the early mild headache phase of an oncoming migraine. Herbal treatment was found to totally relieve pain in 48% of people within 2 hours and a further 34% reported pain had remained mild and not worsened. Of the group, 59% were satisfied with their response to GelStat Migraine therapy (Cady et al 2005). Of note, the product is marketed as a homeopathic product and contains extremely small amounts of both herbs.

Feverfew (100 mg) combined with riboflavin (400 mg) and magnesium (300 mg) was compared to stand-alone riboflavin (25 mg) treatment in a randomised, double-blind study of migraine sufferers (Maizels et al 2004). Both treatments showed a significant reduction in number of migraines, migraine days and migraine index in the 3-month trial, which was greater than responses for placebo in other trials of migraine prophylaxis. When treatment responses were compared, no significant differences were seen between the groups indicating that feverfew at this low dose is ineffective.

Arthritic conditions

Although traditionally used as a treatment for inflammatory joint conditions, the results of a randomised, double-blind study involving 41 patients with symptoms of rheumatoid arthritis (RA) found no difference between chopped dried feverfew (70–86 mg) or placebo after 6 weeks' treatment (Pattrick et al 1989).

OTHER USES

Dermatology

Parthenolide-free feverfew extract is being investigated in various dermatological conditions. It protects skin against inflammation and UV-induced damage (Finkey et al 2005) When the parthenolide-free feverfew extract was topically applied, it significantly reduced the loss of cell viability, the increase in proinflammatory mediator release and the induction of DNA damage induced by solar-simulated UV radiation in a human epidermal model. It also exhibited potent antioxidant activity in vitro and has been shown to dismutate superoxide, thereby protecting cells from the pro-oxidant

depletion of endogenous skin antioxidants. In the next phase of testing, a clinical study was conducted with an emollient containing the parthenolide-free feverfew extract, which confirmed that treatment significantly reduced the erythema effects of acute EVB exposure by up to 60% compared to placebo. Assessment was done by a blinded clinical grader and a chromameter. These results suggest that topical application of parthenolide-depleted feverfew extract can protect skin from UV-induced damage and from oxidative damage and help to repair damaged DNA.

Oncology

Parthenolide has demonstrated potent antitumour activity in a variety of experimental models (in vitro and in vivo), and its mechanisms of action are becoming better elucidated. The positive results obtained in these preliminary studies indicate that it may have potential in the treatment of cancer; however, no clinical studies have been published to date to determine its efficacy in humans.

Traditional use

Feverfew has been used traditionally to treat coughs and colds, fevers, atonic dyspepsia, worm infestation, menstrual disorders, nervous debility, joint pain and headaches. It has also been used to promote expulsion of the placenta after childbirth.

DOSAGE RANGE

- Dried leaf: 50–200 mg daily.
- Fresh plant tincture (1:1): 0.7–2.0 mL/day.
- Dried plant tincture (1:5): 1–3 mL/day.
- Prevention of migraine headaches (based on clinical studies): 125–600 mg/day of powder, standardised to contain a minimum parthenolide content of 0.2%, or 400 microgram, which should be taken for at least 4 months. It is still controversial as to whether standardised extracts are best for migraine prophylaxis or not.

TOXICITY

Unknown, although no major safety issues have been identified (Ernst & Pittler 2000).

ADVERSE REACTIONS

According to a Cochrane systematic review of five studies (Pittler & Ernst 2004), feverfew is well tolerated and adverse events are generally mild and reversible. Symptoms were most frequently reported by long-term users and were predominantly mouth ulceration and gastrointestinal symptoms. Contact dermatitis, mouth soreness and lip swelling have also been reported when leaves are chewed. People allergic to the Compositae family of plant, or feverfew in particular, should avoid feverfew products that contain parthenolide, as it is this component which is thought to be the main inducer of the allergic response (Sharma & Sethuraman 2007).

SIGNIFICANT INTERACTIONS

Controlled studies are not available; therefore, interactions are based on evidence of activity and are largely theoretical and speculative.

Anticoagulants

Theoretically, feverfew may increase bruising and bleeding; however, although feverfew inhibits platelet aggregation in vitro and in vivo, no effects were seen in a clinical study (Biggs et al 1982) — observe patients taking this combination.

CONTRAINDICATIONS AND PRECAUTIONS

Hypersensitivity to plants in the Asteraceae (Compositae) (daisy) family (e.g. chamomile, ragweed).

PREGNANCY USE

Contraindicated in pregnancy. An in vitro and in vivo preliminary screen using a rat model suggested that feverfew consumption may have detrimental effects in pregnancy, a finding which needs to be more fully explored in a larger study (Yao et al 2006). Feverfew-treated animals had reduced litter sizes, a greater proportion of smaller fetuses than the control group and increased preimplantation loss indicating maternal and embryonic effects. However, it should be noted that the doses used were 59 times the accepted human dose, and therefore the clinical relevance of the findings are unclear. A full reproductive toxicity study is warranted to determine whether the observed effects are clinically significant.

PRACTICE POINTS/PATIENT COUNSELLING

- Although early studies were positive and showed a preventative effect for migraine headache, not all studies have been positive, which may be related to variations in preparations and dosing. Further research is required to determine its place in practice for this indication.
- Of the studies that have produced positive results for migraine therapy, feverfew reduced severity of symptoms such as vomiting and visual disturbances, but did not alter the duration of an episode.
- Tincture or solid-dose preparations may be better tolerated than chewing the fresh leaves, which have been associated with mouth ulcers and lip swelling in some individuals.
- Traditionally, feverfew has also been used to treat coughs and colds, fevers, atonic dyspepsia, worm infestation, menstrual disorders, nervous debility, joint pain and headaches.
  - Parthenolide-free feverfew shows promise as a dermatological and UV protective agent when used topically.
  - Many preliminary studies with parthenolide confirm that it has potent antitumour activity; however, it has not yet been tested in humans.
- Use is contraindicated in pregnancy.

PATIENTS' FAQs

What will this herb do for me?

Some evidence suggests that feverfew may reduce the frequency and severity of migraine headaches; however, test results are inconsistent. Topical application with parthenolide-free feverfew cream shows promise as a dermatological preparation to

reduce redness after sun exposure and help heal damaged skin.

When will it start to work?

Of those studies producing positive results, it appears that approximately 4 months' continual use may be required; however, in practice, some patients experience benefits within the first 4 weeks.

Are there any safety issues?

Feverfew should not be used in pregnancy or by people with Compositae allergy.

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Fish oils

BACKGROUND AND RELEVANT PHARMACOKINETICS

One of the two human essential fatty acids (EFA) is alpha-linolenic acid (ALA or 18:3n-3), which, due to the position of its first double bond, is classified as an omega-3 essential fatty acid (n-3 EFA). Although mammals have the ability to introduce double bonds into most positions of the fatty acid chain in fat metabolism, therefore producing various unsaturated metabolites, they lack the capacity to insert double bonds at the n-3 and n-6 positions. Consequently, linoleic acid (LA) and alpha-linolenic acid (ALA), which already have the double bond at the n-3 or n-6 position, respectively, are considered essential and must be consumed in the diet. When the EFAs are consumed in this precursor state they follow a pathway of further elongation and desaturation via the action of delta-6- and delta-5-desaturase until they form the 'active' fatty acids: eicosapentaenoic acid (20:5n-3) (EPA) and docosahexaenoic acid (DHA) (22:6n-3), also referred to as the omega 3 long chain polyunsaturated fats (n-3 LCPUFAs).

Fish oils, also known as marine oils, are rapidly absorbed from the gastrointestinal tract and compete with arachidonic acid (AA) for incorporation into phospholipids, particularly of platelets, erythrocytes, neutrophils, monocytes and liver cells (Simopoulos 1999). When stimulated, the cell membranes release polyunsaturated fatty acids (PUFAs), which are then converted into 20-carbon eicosanoids, which have profound and extensive physiological effects. The most active of these metabolites are prostaglandins, prostacyclins and thromboxanes, which affect blood chemistry, muscle contraction, immune function and inflammation. Dietary fats not used in this way are stored in adipose tissue and ultimately oxidised to produce energy. The FA cell membrane profile of different tissues will have varying ratios of EPA and DHA, but generally DHA is considered the major component of phospholipids in the retina, brain, male reproductive tissue and myocardium (Groff & Gropper 2004).

Supplements based on fish liver oils, such as cod and halibut, contain EPA and DHA together with high levels of vitamins A and D. As such, they have additional actions and safety issues, besides those found with traditional marine lipid supplements. This review will focus on the research surrounding those fish oils that are not liver extractions.

CHEMICAL COMPONENTS

Dietary fish contains a number of nutrients important for health, such as several B vitamins, vitamin E, calcium, magnesium and potassium and are an excellent source of protein with a low saturated fat content. Importantly, they also contain the two PUFAs: EPA and DHA. EPA has 20 carbon atoms and 5 double bonds, and DHA has 22 carbon atoms and 6 double bonds. Both are derived from ALA and are considered conditionally essential. The EPA and DHA found in whole fish are predominantly esterified in the *sn*-2 position of triacylglycerols and glyercophospholipids; however, when found in supplements, most commonly exist as ethyl esters (Visioli et al 2003). This minor chemical distinction may explain the speculated superior bioavailability of these fats when derived from the diet as opposed to supplements.

Clinical note — Are ALA-rich oils a worthy substitute for fish oils?

Both EPA and DHA are derived from ALA, so food sources containing ALA are seen as indirect dietary sources. ALA is commonly found in non-hydrogenated canola oil, linseed oil, soybean oil, flaxseed, pumpkin and walnuts. Studies investigating the effects of ALA supplementation have not consistently produced the same positive results as for fish oils, most likely due to inefficient conversion of ALA into EPA and DHA. This is reportedly poor in healthy individuals, with only 5–10% of ALA converted to EPA and 2–5% of ALA converted to DHA (Davis & Kris-Etherton 2003). Consequently, the few foods that contain both EPA and DHA in their preformed state offer a significant advantage over other sources. The most concentrated dietary source of both EPA and DHA is fish oil. (See Flaxseed monograph for further information.)

FOOD SOURCES

Most dietary EPA and DHA are consumed in the form of fish or seafood. Deep sea cold water fish, such as salmon, mackerel, halibut and herring, provide the most concentrated sources. Current Australian estimates of intake indicate inadequate consumption according to WHO standards (Meyer et al 2003).

DEFICIENCY SIGNS AND SYMPTOMS

Based on epidemiological studies, the low levels of n-3 LCPUFAs are associated with:

- fetal alcohol syndrome (DHA) (Horrocks & Yeo 1999)
- attention deficit hyperactivity disorder (DHA) (Horrocks & Yeo 1999)
- learning deficits (DHA) (Horrocks & Yeo 1999)
- cystic fibrosis (DHA) (Horrocks & Yeo 1999)
- phenylketonuria (DHA) (Horrocks & Yeo 1999)
- cardiovascular disease, including an increased risk of sudden death due to heart disease (Siscovick et al 2003).
- inflammatory disorders
- rheumatoid arthritis (Navarro et al 2000)
- unipolar depression (DHA) (Horrocks & Yeo 1999)
- senile dementia

In addition to these symptoms, lack of dietary EFAs has been implicated in the development or aggravation of numerous diseases such as breast

cancer, prostate cancer, RA, asthma, preeclampsia, depression and schizophrenia (Yehuda et al 2005).

Primary deficiency

Full-term babies fed a skim milk formula low in ALA are at risk of primary deficiency. In the past, patients fed long-term with fat-free TPN solutions were at risk, but fat emulsions are now in general use and prevent deficiency. Studies have demonstrated lower plasma levels of EPA and DHA in vegetarians and vegans, suggesting they may be at risk of deficiency; however, the findings of a recent cross-sectional study comparing the dietary intakes and plasma levels of 196 meat-eating, 231 vegetarian and 232 vegan men in the United Kingdom did not suggest that there is cause for alarm (Rosell et al 2005). Vegans and vegetarians had significantly lower levels of these fatty acids; however, they remained steady and there is evidence of some conversion of ALA into EPA and DHA.

There is much discussion regarding the inadequate intake of EPA and DHA generally in the Western diet. Recent Australian data, based on dietary intake records from the 1995 National Nutrition Survey, have estimated the average daily intake of EPA and DHA to be 0.008 g and 0.015 g, respectively. If correct, this indicates that the majority of Australians are failing to meet recommended amounts (Meyer et al 2003).

Secondary deficiency

People with fat malabsorption syndromes, serious trauma or burns are at risk of reduced PUFA levels (Beers et al 2003). A secondary deficiency may also manifest as a result of abnormal or compromised activity of the delta-6 and delta-5 desaturase enzymes, for example in diabetics, patients with a variety of metabolic disorders and individuals with increased dietary saturated fats and *trans* fatty acids, alcoholics and the elderly (Davis & Kris-Etherton 2003, Houston 2005).

MAIN ACTIONS

As precursors of eicosanoids, PUFAs found in fish oils exert a wide influence over many important physiological processes.

Cardiovascular effects

Fish oils exert myriad different effects on the heart and vessels, demonstrated in both experimental models and human studies. It is speculated that the clinical effects attributed to n-3 PUFA are due to the summation of many small pharmacological effects, adding up to a larger protective effect on mortality and/or cardiovascular events.

Prevent malignant cardiac arrhythmias

Dietary fish or fish oil intake has been shown to prevent cardiac arrhythmias and associated sudden death in numerous animal studies (Billman et al 1997, 1999, Kang & Leaf 1996, 2000, McLennan et al 1988, 1990), in vitro and more recently human clinical trials (Jung et al 2008). This has been achieved using intakes below those required to alter plasma lipids or blood pressure. It appears that the myocardial membrane phospholipid content increases in DHA but not always EPA, with fish intake. The preferential accumulation of DHA affords protection against ventricular fibrillation induced under a variety of conditions such as ischaemia and reperfusion (McLennan 2001).

Inadequate DHA in myocyte membranes has been reported to be associated with altered sodium, calcium and potassium ion channel functions, mitochondrial function and increased arrhythmia susceptibility with an increased prevalence of sudden cardiac death (Jung et al 2008, Siscovick et al 2003). One in vivo study suggests that fish oils electrically stabilise myocytes, increasing the electrical impulse required to produce an action potential by approximately 50% and prolonging the refractory time by 150% (Kang & Leaf 2000).

Triglyceride (TG)-lowering activity

Fish oil supplements effectively reduce TG levels as demonstrated in human studies. This is of particular interest, given only moderate elevations in TG levels have been associated with a progressively increased risk of ischaemic heart disease, independent of other major risk factors, including HDL cholesterol (Jeppesen et al 1998).

Lipoprotein effects

Both n-6 and n-3 LCPUFAs can inhibit the expression of genes involved in fatty acid and TG synthesis (Jung et al 2008). Dietary n-3 LCPUFAs, in particular, and their metabolites, through this mechanism are reported to increase beta-oxidation and inhibit adipogenesis. Ultimately, this may result in reduced substrate for TG synthesis and thus explain n-3 PUFAs' profound TG-lowering effects.

Concerns raised previously about increased LCPUFAs in lipoproteins increasing the susceptibility to oxidation of the LDLs have recently been moderated, with a demonstrable difference between EPA and DHA. While increased levels of EPA (4.8 g/day) did increase the LDL susceptibility to damage, DHA supplementation (4.9 g/day) had no effect on the oxidation process (Mesa et al 2004). Concurrent supplementation with antioxidants however appears prudent with high doses of n-3 PUFAs.

Improved endothelial function

Studies have indicated that fish oils can improve endothelial relaxation by enhancing NO- and non-NO-induced vasodilatation (Holub 2002).

A double-blind study conducted by Mori et al (2000) showed that relative to placebo, DHA, but not EPA, enhances vasodilator mechanisms and attenuates constrictor responses in forearm microcirculation.

Reduce blood pressure

Two meta-analyses have concluded that fish oils exert a significant blood pressure-lowering effect in hypertensive people; however, the effects can only be described as modest, between 2 and 5 mmHg (Geleijnse et al 2002, Morris et al 1993). Hypotensive activity appears to be dose-dependent

Clinical interest — Do fish oil supplements cause bleeding?

A search through Medline reveals several case reports where bleeding episodes are attributed to fish oil ingestion (Buckley et al 2004, Jalili & Dehpour 2007, McClaskey & Michalets 2007). In each case, the person affected was elderly and also taking warfarin. One was a report of an elderly man taking high-dose omega-3 fatty acids (6 g/day) with both aspirin and warfarin who developed a subdural haematoma after a minor fall (McClaskey & Michalets 2007). Another case is reported of a 67-year-old woman taking warfarin for 1.5 years who doubled the fish oil dose from 1000 to 2000 mg/day causing an associated elevation in INR from 2.8 to 4.3 within 1 month (Buckley et al 2004). A third case was of a 65-year-old male who had been taking warfarin for 6 months and then was recommended trazodone and fish oils causing his INR to rise to 8.06 (Jalili & Dehpour 2007).

Although these case reports would lead us to believe that omega-3 fatty acids interact with warfarin and increase the risk of bleeding, several intervention studies have come to a different conclusion. One randomised study of 511 patients taking either aspirin (300 mg/day) or warfarin (INR aimed at 2.5–4.2) found that a dose of 4 g/day of fish oils did not increase the number of bleeding episodes, bleeding time or any parameters of coagulation and fibrinolysis (Eritsland et al 1995). A smaller placebo-controlled study by Bender et al of patients receiving chronic warfarin therapy found that fish oils doses of 3–6 g/day produced no statistically significant difference in INRs between the placebo lead-in and treatment period within each group. There was also no difference in INRs between groups (Bender et al 1998).

Most recently, Harris examined 19 clinical studies which used doses of fish oils varying from 1 g/day to 21 g/day in patients undergoing major vascular surgery (coronary artery bypass grafting, endarterectomy) or femoral artery puncture for either diagnostic cardiac catheterisation or percutaneous transluminal coronary angioplasty (Harris 2007). Of note, in 16 studies patients were taking aspirin and in three studies patients were taking heparin. The review concluded that the risk for bleeding was virtually non-existent. Frequent comments accompanying the studies were 'no difference in clinically significant bleeding noted' or 'no patient suffered from bleeding complications'. The same conclusion was reached in a 2008 review which stated no published studies have reported clinically significant bleeding episodes amongst patients treated with antiplatelet drugs and fish oils (3–7 g/day) (Harris et al 2008).

Overall, when we consider the body of evidence available regarding omega-3 fatty acid supplementation, it is clear that the benefits for cardioprotection far outweigh the risk of bleeding. This not only applies to patients taking aspirin but also those patients about to undergo coronary artery bypass surgery or percutaneous transluminal coronary angioplasty. Whilst the evidence suggests that fish oils in low to moderate doses do not increase bleeding risk with warfarin, a general caution should still apply to patients taking high doses.

and DHA may have greater effect than EPA. Alternately, a 2006 Cochrane review found no significant changes to SBP or DBP with n-3 LCPUFAs consumption (Hooper et al 2006). The review assessed studies that used both plant- and fish-based n-3 fatty acids, dietary sources and supplements.

While the mechanism is unknown, current theories include EPA stimulation of prostacyclin synthesis and increased NO production — both vasodilators. An additional action may be improved autonomic nervous system function, and inhibition of the adrenal activation (Din et al 2004, Ross 2005); however, these are inconsistent with the attribution of action to DHA. In addition to the actions improving endothelial function generally, other posited mechanisms for a hypotensive effect include: blunting of the rennin–angiotensin–aldosterone system via reduced adrenal aldosterone synthesis, altered arachidonic acid metabolism, modulation of calcium release and influx into vascular smooth muscle cells and activation of vascular adenosine triphosphate (ATP)-sensitive potassium channels (Jung et al 2008).

Reduce and possibly reverse atherogenesis

Omega-3 fatty acids alter eicosanoid synthesis and inhibit smooth muscle cell proliferation, suggesting a role in reducing atherosclerotic development (Holub 2002). One controlled study demonstrated that fish oil ingestion had a clinically significant influence on atherosclerosis (von Schacky et al 2001). This randomised, double-blind study of 223 patients found that a dose of 1.5 g n-3 fatty acids reduced progression and increased regression of established coronary artery disease as assessed by coronary angiography.

Antithrombotic and antiplatelet

Dietary n-3 PUFAs enhance anti-aggregatory and anti-adhesive platelet activity by inducing increased production of prostacyclin I_3 and suppressing synthesis of the chemotactic platelet adhesion-promoting substances, leukotriene B4 and thromboxane A_2 (Jung et al 2008, Kinsella 1987). Independent of this, n-3 LCPUFAs reduce levels of several coagulating factors (e.g. VII and X, and fibrinogen) (Jung et al 2008).

In animal models of arterial thrombosis, fish oil-enriched diets have been shown to have an antithrombotic effect; however, there is evidence suggesting that this is most likely to occur when associated with reduced saturated fat intake (Hornstra 1989).

Clinical observations of Eskimos have found lowered platelet counts, inhibition of platelet aggregation and prolonged bleeding times compared

with age- and sex-matched Danes. However, intervention studies using fish oil supplements have produced conflicting results (Hellsten et al 1993, Kristensen et al 1989, Radack et al 1990) and more recently, a review of clinical studies concluded that there was no clinically significant effect on bleeding with usual therapeutic doses (Harris 2007).

Anti-inflammatory

Fish oils induce a series of chemical changes in the body that ultimately exert an anti-inflammatory action. They partially replace AA in inflammatory cell membranes, and compete with it for the enzymes cyclo-oxygenase (COX) and lipoxygenase (LOX), leading to reduced production of proinflammatory metabolites such as 2-series PGs and 4-series leukotrienes (Calder 2002, 2003, Cleland et al 2003).

Besides this, n-3 PUFAs suppress the production of proinflammatory cytokines, and reduce the expression of cell adhesion molecules, critical in recruiting circulating leucocytes to the vascular endothelium (Calder 2002, Din et al 2004). According to new research, it appears that anti-inflammatory activity may vary among different sources of fish oils due to variations in EPA/DHA content (Bhattacharya et al 2006).

Neurological effects

Fatty acids are major components of the brain and are found in high concentrations in two structural components: the neuronal membrane and the myelin sheath. About 50% of the neuronal membrane is composed of fatty acids (1/3 from n-3 LCPUFAs), while in the myelin sheath lipids constitute about 70% (Yehuda et al 2005). The lipid component has a relatively high turnover, in contrast to the protein component, which is fundamentally stable.

Omega-3 fatty acids play an active role in neuronal membrane function, fluidity and control of neuronal growth factors. They also potentially influence each step in biogenic amine function, including neurotransmitter synthesis, degradation, release, reuptake and binding (Bruinsma & Taren 2000). Studies indicate that dietary PUFAs may influence noradrenergic and serotonergic neurotransmission and receptor function in the nervous system and, thereby, have a direct effect on function, mood and behaviour. Other actions at the neuronal cell membrane include suppression of the phosphatidyl-associated signal transduction pathways, blocking of the calcium ion influx through L-calcium channels and direct inhibition of protein kinase C, which are similar actions to those exhibited by pharmaceutical mood stabilisers.

Prenatal and postnatal neurological development

DHA plays an important, if not critical, role in the growth and functional development of the brain during the third trimester and the early postnatal period when maximal growth occurs (Horrocks & Yeo 1999). Given that 15% of brain growth occurs during infancy, much attention has been paid to the consequences of variable n-3 levels during late pregnancy and early infancy. It also plays an important role in retinal development, where DHA constitutes 60% of total PUFAs.

Chemopreventative effects

Marine fatty acids, particularly EPA and DHA, have been consistently shown to inhibit the proliferation of breast and prostate cancer cell lines in vitro and to reduce the risk and progression of these tumours in animal experiments (Bagga et al 2002, Terry et al 2003). Similar effects have also been observed for colorectal and prostate cancers (Calder et al 1998, Llor et al 2003, Stoll 2002).

Chemopreventative actions demonstrated by n-3 LCPUFAs include suppression of neoplastic transformation, cell growth inhibition and enhanced apoptosis and anti-angiogenicity (Rose & Connolly 1999). The proposed mechanisms for these are extensive, including the suppression of n-6 eicosanoid synthesis; influences on transcription factor activity, gene expression, and signal transduction pathways; effects on oestrogen metabolism; increased or decreased production of free radicals and reactive oxygen species, and influences on both insulin sensitivity and membrane fluidity (Larsson et al 2004). Ongoing research is attempting to elucidate the specific chemopreventative mechanisms of fish oils with the individual cancer cell lines.

CLINICAL USE

Thousands of studies have been conducted in various populations to determine the clinical consequences of regular fish consumption or fish oil supplementation. Some have focused on n-3 fatty acids intake as a whole and included both vegetable and marine-based sources; however, in light of the lack of bioequivalence and clinical efficacy between the n-3 precursors (e.g. ALA) and their long chain derivatives (e.g. EPA/DHA), the results of these studies are likely to be confounded. Similarly, early study designs investigating the effects of n-3 PUFAs often produced inconsistent results due to improper placebo selection (e.g. olive oil). While these oils were considered at the time to be inert, our progressive understanding of EFA metabolism attributes such 'placebos' with actions of their own, again confounding the results (Pizzorno & Murray 2006). It is important to note that few studies or reviews have also considered the effect of variations in n-3:n-6 ratio which may be important.

Prevention of morbidity and mortality of cardiovascular disease

For over 25 years, fish and fish oils have been linked to cardiovascular health. This association was first recognised when significantly lower death rates from acute myocardial infarction (MI) were found among Greenland's Inuit population, despite only moderate differences between the Inuits' blood cholesterol levels and those of other populations (Holub 2002). A high dietary n-3 LCPUFAs intake in the form of marine mammals (seal, whale) and various fish were thought to be responsible for the protective effect (Bang et al 1980). In 1989, results from the first large, randomised, clinical trial investigating the effects of fatty fish consumption

on survival and risk of secondary MI confirmed a link to cardiovascular health (Burr et al 1989). The Diet and Reinfarction study (DART) found that a modest intake of 2–3 portions weekly of fatty fish reduced mortality in men who had previously experienced a MI and produced a relative reduction in total mortality of 29% during the 2-year follow-up, attributed mainly to a reduction in deaths from coronary heart disease (CHD). Increased consumption of fish (RR = 0.66 for five or more times per week) was further confirmed in the Nurses Study as significantly reducing risk in both CHD and CHD-related mortality independent of the cardiovascular status (Hu et al 2002).

Various epidemiological trials and intervention studies have also been conducted to investigate the association between fish consumption and CVD and whether similar or superior effects could be obtained with concentrated fish oil supplements. Overall, epidemiological and interventional approaches have clearly demonstrated that individuals with a diet rich in fish (30–35 g/day) or supplemented with EPA and DHA (up to 665 mg/day) show a 30–50% reduction in CHD and CHD-related mortality compared to individuals who did not eat fish (Russo 2009). It appears that whilst primary CVD prevention occurs, secondary prevention effects are more notable.

Not surprisingly, in 2004, the FDA reported that it would allow products containing omega-3 fatty acids to claim that eating the product may reduce the risk of heart disease. The FDA based its decision on the wealth of scientific evidence that suggests a correlation between omega-3 fatty acids such as EPA and docosahexaenoic acid and a reduced risk of coronary artery disease (CAD). The FDA subsequently approved omega-3 fatty acids as a treatment to reduce plasma TGs (Frishman et al 2009).

The largest study is known as the GISSI trial, which involved 11,324 survivors of MI, demonstrating that a low-dose fish oil supplement significantly reduced the risk of all-cause death, non-fatal MI and non-fatal stroke (Stone 2000). This study was re-analysed and subsequently published again in 2002 (Marchioli et al 2002). This time it specifically showed that the reduction in risk of sudden cardiac death was nearly significant at 3 months, accounting for 67% of the overall mortality benefit, became significant at 4 months, and was highly significant at 3.5 years, the end of the study, when it accounted for 59% of the n-3 PUFA advantage in mortality. The reduction observed in all-cause mortality and in cardiovascular mortality resulted mainly from the prevention of sudden cardiac death by the n-3 LCPUFAs.

Meta-analyses

In 2002, a high-quality systematic review of 11 RCTs on the effect of fish-based dietary or supplemental omega-3 fatty acids on cardiovascular morbidity and mortality in people with CHD found a strongly significant benefit (Bucher et al 2002); however, a 2006 Cochrane review came to a different conclusion (Hooper et al 2006). The review assessed 48 studies that compared at least 6 months of omega-3 fats (vegetable- and fish-based) with placebo or control and used data involving 36,913 participants. Meta-analysis of the studies assessing the effects of increased omega-3 fats on total mortality or combined cardiovascular events found strongly significant statistical heterogeneity. When randomised studies considered to be at medium or high risk of bias were removed, there was no significant effect of omega-3 fats on total mortality; the relative risk was 0.87 (95% confidence interval 0.73 to 1.03, with significant heterogeneity), whereas the cohort studies suggested significant protection, the relative risk was 0.65 (95% confidence interval 0.48 to 0.88, no significant heterogeneity).

It is important to note that until the publication of the DART-2 trial in 2003 (Burr et al 2003), the evidence showed that omega-3 from oily fish or supplements reduced the risks of fatal MI, sudden death and overall mortality among people with existing disease. Inclusion of the DART-2 trial in the Cochrane review had a major influence on the conclusion, as removing it produced relative risks similar to those in the Bucher review (fatal MI: RR 0.70, 95% confidence interval 0.54 to 0.91; sudden death: RR 0.68, 95% confidence interval 0.42 to 1.10; overall mortality: RR 0.83 (95% confidence interval 0.75 to 0.91). The DART-2 trial included 3114 men with stable angina and tested the hypothesis that the main benefit of omega-3 fat is derived from its anti-arrhythmic action in the presence of chronic disease. Surprisingly, it did not confirm this, showing an excess of sudden and total cardiac deaths most clearly in participants taking fish oil capsules rather than eating oily fish. Authors of the Cochrane review report that something about the DART-2 study is different from the other included studies; however, further investigation has failed to clarify the issue. It is possible that, based on this latest review, the effect of omega-3 fats on CVD is smaller than previously thought or that effects in people who have had a MI are protective, but the effects in men with angina and no MI are not.

Congestive heart failure

In 2005, an association between the consumption of tuna or other broiled or baked fish (but not fried) and lower incidence of CHF was observed among older adults (Mozaffarian et al 2005). In 2008, a large, placebo-controlled trial in patients with CHF (GISSI-HF) demonstrated that the use of 1 g of omega-3 essential fatty acids was associated with a statistically significant 9% reduction in all-cause mortality (Tavazzi et al 2008). The double-blind study involved patients (n = 6975) with chronic heart failure of New York Heart Association class II–IV.

Patients with implantable cardioverter defibrillators (ICDs)

Patients with ICDs administered 2.6 g/day of combined EPA and DHA in one study demonstrated significantly increased time to first ICD event for ventricular tachycardia, fibrillation or death (Jung et al 2008). However, not all studies have produced such positive results, with some suggesting that the n-3 LCPUFAs are ineffective in this patient group (Jenkins et al 2008, Nair & Connolly 2008).

Clinical note — The n-3:n-6 balance: implications in cardiovascular disease and cancer

In recent years, attention has been drawn to the importance of not only n-3 fatty acid intake but also its relation to concurrent n-6 fatty acid intake (Simopoulos 2008). When there is increased n-3 LCPUFAs in the diet and in our bodies, a shift in AA metabolism occurs, which results in the production of metabolites that have beneficial effects on cardiovascular physiology and cancer incidence and promotion (Leaf 2002). For example, when EPA is available to compete with AA, production of thromboxane A2 (a potent vasoconstrictor and platelet activator) is reduced and production of thromboxane B3 results, which is only weakly active. Additionally, several forms of research implicate n-6 PUFAs as stimulating processes that promote human cancer development and progression, whereas n-3 LCPUFAs have the opposite effect (Weisburger 1997). Once again, competition with AA is thought to be involved, although several other protective mechanisms have also been identified. Overall, it seems that in order to obtain maximal cardiovascular and chemopreventative benefits, intake of n-3 LCPUFAs should be increased and intake of n-6 PUFAs must be reduced.

It has been estimated that the ratio of n-6 to n-3 essential fatty acids in the Western diet is some 15:1 to 20:1 or higher, whereas the optimal ratio appears to be closer to 2:1 or 1:1 (Leaf 2002, Simopoulos 1999, 2008).

Elevated TG levels

DHA and EPA supplementation significantly reduces TG levels in both normo- and hyperlipidaemic individuals and is used as sole therapy in cases of elevation or as adjunctive therapy with cholesterol-lowering medication when indicated. Omega-3 LCPUFAs reduce TG concentrations in a dose-dependent manner, with intakes approximating 4 g/day lowering serum TGs by 25–30% in patients hyperlipidaemic at baseline (Balk et al 2006, Din et al 2004, Jung et al 2008). Recently, studies have emerged using n-3 LCPUFA in combination with statins for the treatment of hyperlipidaemia (Barter & Ginsberg 2008). While LDL reduction is the primary target of statins, fish oil co-supplementation both enhances this action and produces additional beneficial changes in other lipid parameters (e.g. HDL, TGs and lipoprotein particle size).

Overall, it appears that the smallest amount of n-3 LCPUFAs required to lower serum TG levels significantly is approximately 1 g/day, as provided by a fish diet, or as little as 0.21 g EPA and 0.12 g DHA/day for those with hyperlipidaemia (Weber & Raederstorff 2000).

Hypertension

According to two meta-analyses, fish oils have a significant but modest dose-dependent effect on blood pressure in hypertension (Geleijnse et al 2002, Morris et al 1993). The DHA component is likely to have stronger effects than EPA. In contrast, a 2006 Cochrane review found no significant changes to SBP or DBP with n-3 EFA consumption of vegetable or fish origin (Hooper et al 2006).

The first meta-analysis was of 31 placebo-controlled trials involving 1356 subjects and detected a statistically significant dose–response effect on blood pressure when studies were grouped by omega-3 fatty acid dose: –1.3/–0.7 mmHg at doses ≤3 g/day, –2.9/–1.6 mmHg at 3.3–7 g/day, and –8.1/–5.8 mmHg at 15 g/day (Morris et al 1993). The hypotensive effect was strongest in hypertensive subjects and those with clinically evident atherosclerotic disease or hypercholesterolaemia, whereas no effect was detected in healthy subjects.

The 2002 meta-regression analysis considered the results from 36 trials, of which 22 had a double-blind design, to determine whether fish oil had a significant effect on blood pressure (Geleijnse et al 2002). Fish oil intake (median dose: 3.7 g/day) was found to reduce SBP by 2.1 mmHg and DBP by 1.6 mmHg when all trials were considered. When restricted to double-blind studies only, effects were not as large, but still apparent. Overall, the effects of fish oil on blood pressure tended to be greater in older people (>45 years) and in hypertensive populations (BP ≥140/90 mmHg).

More recent studies have produced comparable results with doses of 3–5.6 g/day associated with reductions of 5.5 mmHg and 3.5 mmHg in systolic and diastolic pressures, respectively (Jung et al 2008). Another meta-analysis of 30 RCTs found that fish oil supplementation reduced heart rate by 1.6 beats/min.

Prior to cardiac surgery

Whilst many secondary coronary heart disease prevention trials require months of treatment before the benefits of omega-3 fatty acid supplementation are detected, a clinical study with cardiothoracic surgical patients suggests acute benefits within weeks. Calo et al conducted a randomised, placebo-controlled study which found that patients taking 2 g/day of fish oils for at least 5 days prior to coronary artery bypass grafting and until discharge had a significantly reduced incidence of postoperative atrial fibrillation (AF) (Calo et al 2005). Specifically, 15.2% of patients receiving fish oils experienced postoperative AF compared with 33.3% of patients who were not taking the supplement. In addition, hospital length of stay was significantly reduced by one day. Except for a single case of allergy, no adverse effects were observed.

Intermittent claudication

A recent Cochrane review of six studies involving 313 subjects suffering from intermittent claudication and treated with n-3 LCPUFAs (typical dose 1.8 g EPA and 1.2 g DHA per day) over weeks to years found that, in spite of some haematological improvements (e.g. reduced viscosity), there were no demonstrable improvements in clinical outcomes (Sommerfield et al 2007).

Clinical note — Would you like methylmercury (MeHg) or organohalogen pollutants (OHPs) with that?

In aquatic environments, inorganic mercury, either naturally occurring or as an industrial by-product (e.g. coal-fired power plants, waste incinerators), is converted into MeHg by microorganisms present in sediment or within the intestine of fish themselves (Dorea 2006). The MeHg, which is the most hazardous dietary form, then accumulates in the aquatic food chain, making fish the primary source of exposure for most individuals (FSANZ 2004). There has been increasing public awareness and concern regarding MeHg exposure secondary to fish consumption. This has been partly in response to the health warnings issued by Food Standards Australia and New Zealand (FSANZ) in March 2004 regarding maximal intake of selected fish species during pregnancy and childhood (Bambrick & Kjellstrom 2004). Interestingly, while the main public concern relates to neurodevelopmental toxicity, emerging data show a relationship between increasing MeHg exposure and cardiovascular disease, in particular MI (Stern 2005). Postulated mechanisms include the oxidative stress and reactive oxygen species observed with in vitro exposures to MeHg, as well as impaired calcium homeostasis and kidney function.

MeHg concentrations in fish and shellfish species, which represent 80–90% of the mercury present, range from <0.1 ppm for shellfish, such as oysters and mussels, to multiple parts per million in large predatory fish such as tuna, marlin, swordfish and shark. Consequently, MeHg intake depends on the species and age of fish consumed, as well as the quantity eaten. Previous American data determined that adults consumed an average of 18 microgram MeHg/day, with 80–90% coming from fish and shellfish (Mahaffey et al 2004).

Inorganic mercury is readily excreted in the urine, whereas MeHg accumulates in erythrocytes across a wide range of exposures (Mahaffey et al 2004). Multiple international studies assessing MeHg exposure levels have revealed that approximately 10% of blood samples were high. American studies have identified populations at greater risk, among them a subpopulation consuming a substantial amount of fish in pursuit of health benefits. Blood MeHg analysis revealed blood mercury levels up to 90 microgram/L (Hightower & Moore 2003). This is concerning given levels >5 microgram/L have been reported as potentially detrimental in women of childbearing age.

Some researchers propose that the potentially cardiotoxic effects of MeHg is countered by the presence of the omega-3 oils also found within fish, and interestingly there is some overlap between those species with the highest concentrations of both (Bambrick & Kjellstrom 2004). However, there is also concern that the converse is true and MeHg could counteract the health-giving benefits of fish.

While fish oil supplements are not a major source of mercury and as such there is no need to restrict their intake (Bays 2007, FSANZ 2004, Levine et al 2005, Schaller 2001), OHPs such as polychlorinated biphenyls (PCBs), dioxins, organochlorine pesticides etc., widely used in flame retardants, pesticides, paints, electrical equipment etc, prior to their ban in the 1980s in most countries (Bays 2007) may be present in these products. OHPs also accumulate in the aquatic food chain and are lipophilic carcinogens as well as being associated with other health risks (Dorea 2006). Data across the board confirm significantly higher OHPs in farmed fish and the supplements produced from these (Jacobs et al 1998, 2004) compared with wild harvested samples. These higher levels are attributed most consistently with use of contaminated feed (Domingo & Bocio 2007, Dorea 2006, Easton et al 2002, Jacobs et al 2002, Melanson et al 2005).

A UK study analysing the OHP content of 21 commercially available fish (both whole body fish and cod liver oil) and vegetable oil dietary supplements in 2004 found that levels in all fish oil products had increased dramatically in brands tested 8 years previously (Jacobs et al 1998, 2004). For example, OHP levels in cod liver oils, which originally ranged from 0–13 ng/g were found to contain 15–34 ng/g in the most recent analysis. The findings of an American study contrast with this, however, with OHP levels below the level of detection in five over the counter fish oil products (Melanson et al 2005). There is no published data on Australian products.

There remains little doubt that the discriminating inclusion of fish is an important part of a healthy diet while several risk/benefit analyses of fish intake at currently recommended levels have recently been published (Domingo 2007, Foran et al 2005, Mozaffarian & Rimm 2006). Many of these make a distinction between the consumption of farmed and wild varieties, with researchers concluding that some of the benefits of increased fish consumption may be negated by the high level of OHPs found in the former, which elevate cancer risk (Foran et al 2005, Mozaffarian & Rimm 2006, Tacon & Metian 2008). A smaller number of papers have specifically considered the risks associated with fish oil supplementation, concluding that their net effect is still a health-promoting one (Bays et al 2007, Melanson et al 2005).

Neurological effects

There is evidence that alterations to n-3 fatty acid metabolism and the composition of the phospholipids in serum and membranes are involved in the pathogenesis of some neurological disorders (Ulbricht & Basch 2005). Also, several epidemiological studies have reported low-plasma DHA status in individuals with schizophrenia, attention-deficit hyperactivity disorder (ADHD), dyslexia, personality disorder, depression and bipolar disorder (Riediger et al 2009). As a result, there has been much interest

in understanding the effects of supplemental n-3 fatty acids in neurological development, cognitive function, behavioural problems and other neurological conditions.

Cognitive function

Low-serum DHA level is considered a significant risk factor for the development of Alzheimer's dementia (Conquer et al 2000). Additionally, both DHA and total n-3 LCPUFAs are significantly lower in cognitively impaired but non-demented people and people with other dementias. One of the first interventional studies was a small RCT of 4.3 g/day DHA in 20 elderly nursing home residents, assessing the efficacy of fish oil in the treatment of vascular dementia. DHA supplementation resulted in a small improvement in dementia rating scores within 3 months of treatment (Terano et al 1994).

The results from numerous animal studies, demonstrating neuroprotection and slowing of neurodegeneration from the n-3 LCPUFAs, appear promising (Hashimoto et al 2005, Mucke & Pitas 2004); however, more clinical trials are required to confirm these positive findings.

Alzheimer's dementia

Epidemiological studies have shown that dementia and CVD may share several common risk factors, including high intakes of dietary total fat, high saturated fat, high n-6:n-3 fatty acid ratio, and low fish intake (Riediger et al 2009). Considering n-3 fatty acids possess anti-inflammatory properties and inflammatory markers have been located in the brain of patients with Alzheimer's disease, it seems reasonable to suggest that n-3 fatty acids may delay the onset of Alzheimer's disease by reducing brain inflammatory state. This may be one of the reasons behind prevention of Alzheimer's disease/dementia by adequate DHA/EPA intake suggested by the Framingham heart study (Kalmijn 2000, Kalmijn et al 2004), the Rotterdam study (Kalmijn et al 1997) and the 2003 prospective study by Morris et al (Morris et al 2003) although later follow-up of the Rotterdam study found no association (Engelhart et al 2002).

In 2005, a review of the evidence prepared for the US Department of Health and Human Services concluded that there is a significant correlation between fish consumption and reduced incidence of AD. Total n-3 LCPUFA and DHA consumption correlated with this risk reduction; however, ALA and EPA did not (Maclean et al 2004). A Cochrane review came to a similar conclusion, reporting that there is a growing body of evidence from biological, observational and epidemiological studies to suggest a protective effect of n-3 LCPUFAs against dementia; however, further research is required before firm conclusions can be made (Lim et al 2006). A recent study investigating supplementation with 1.8 g/day of fish oils over 24 weeks in subjects with either mild-to-moderate Alzheimer's disease or mild cognitive impairment yielded greatest benefits in individuals suffering only mild cognitive impairment (Chiu et al 2008). Further studies using higher doses, larger sample sizes and only subjects mildly affected by the condition are recommended.

Autism

Two studies have found evidence of low levels of EPA and DHA in autistic patients (Curtis & Patel 2008). Despite this, surprisingly few studies have investigated the effects of n-3 LCPUFAs in autistic individuals. One study conducted in a sample of 12 children, employing 5 g/day of n-3 LCPUFAs over 6 weeks, produced significant remission of hyperactivity (Amminger et al 2007), while a more recent one using comparable doses in adults failed to demonstrate efficacy on any behavioural parameter (Politi et al 2008). The data obtained from research based on an online survey of 861 parents of autistic children suggests that consumption of a formula devoid in DHA and AA during infancy is associated with an OR of 4.41 for autism generally and 12.96 for regressive autism, compared with breastfed infants (Schultz et al 2006). However, the heavy reliance upon self-reporting in addition to the non-random sample leave these results open to scrutiny.

Pregnancy, breast feeding and infants

Although numerous studies of mothers and infants have demonstrated that consuming greater amounts of EFAs had a positive effect on the subsequent cognitive development and IQ of their young offspring (Cohen et al 2005, Helland et al 2003, Williams et al 2001), the Evidence Report/Technology Assessment prepared for the Agency of Healthcare Research and Quality of the US Department of Health and Human Services concludes that, based on the small number of current well-designed studies, there is no conclusive evidence of any benefit (Moher 2005). The report makes the observation that studies demonstrating a positive relationship between n-3 LCPUFAs and cognition are those that assessed children under 1 year of age, whereas in studies of older children a significant statistical relationship is not sustained. Despite the conclusions of this report, several studies with longer follow-up periods have demonstrated both improved eye and hand coordination (Dunstan et al 2008) and IQ at 4 years old (Helland et al 2003), but not at 7 (Helland et al 2008). The latter is a recent Australian study, following up on 98 women who were supplemented with 2.2 g DHA and 0.1 g EPA per day or placebo from 20 weeks gestation. Children's eye and hand coordination scores correlated with n-3 LCPUFA levels in cord blood RBC and inversely correlated with n-6 LCPUFA at 2½ years of age.

According to the WHO and FAO, the pregnant woman should take at least 2.6 g of n-3 EFAs, incorporating 100–300 mg of DHA, daily to look after the needs of the fetus (Bambrick & Kjellstrom 2004). Postnatal deficiencies have been associated with reduced visual acuity, poor neurodevelopment and ill effects on behaviour. Breast-fed infants generally receive sufficient DHA if the maternal diet is adequate, but it is not known whether formula-fed

infants receive adequate amounts if their formula does not contain PUFAs.

Preventing depression

After adjusting for several confounding factors, Kamphuis et al reported that every 50 mg/day increase in n-3 fatty acid intake was correlated with a 7% risk reduction of depressive symptoms in elderly men (Kamphuis et al 2006). It has been suggested that the balance between n-6 and n-3 EFA influences the metabolism of biogenic amines, an interaction that may be relevant to changes in mood and behaviour (Bruinsma & Taren 2000). In several observational studies, low concentrations of n-3 LCPUFAs predicted impulsive behaviours and greater severity of depression. Additionally, early research by Horrobin et al (1999) revealed that almost all studies on depression have found increased PG_2 series or related thromboxanes and there is evidence that the older antidepressants (i.e. MAOIs and TCAs) either inhibit PFG synthesis or are powerful antagonists of their actions. The findings of a number of studies showing a correlation between low erythrocyte n-3 EFAs and suicide attempts go one step further. One demonstrated an eightfold difference in suicide attempt risk between the lowest and highest RBC EPA quartiles (Huan et al 2004). Belgian researchers have also speculated about seasonal variations in EFA status that correlates with seasonal patterns of suicide (De Vriese et al 2004); however, studies on larger populations of depressed people are required to confirm this link.

Treating depression

In spite of a plethora of epidemiological data correlating n-3 status with a range of depressive disorders, including major depression, postpartum depression and seasonal affective disorder, there are relatively few interventional studies. In addition to this, those published are typically compromised by small sample size and possess heterogeneous designs, particularly with regard to the composition and dose of the intervention itself (Grenyer et al 2007). Initial studies utilised products rich in EPA, while more recent studies have investigated DHA-rich preparations. There appears to remain much uncertainty regarding both the active ingredient and the optimal dose in the management of depression.

Peet and Horrobin studied 70 patients with treatment-resistant depression randomised on a double-blind basis to placebo or ethyl-eicosapentaenoate at dosages of 1, 2 or 4 g/day for 12 weeks. Patients continued standard medication during the study. The 1-g/day group showed a significantly better outcome than the placebo group on all three rating scales. The 2-g/day group showed little evidence of efficacy, whereas the 4-g/day group showed non-significant trend towards improvement. All of the individual items on all three rating scales improved with the 1-g/day dosage of ethyl-eicosapentaenoate compared to placebo with strong beneficial effects on items rating depression, anxiety, sleep, lassitude, libido and suicidality (Peet & Horrobin 2002).

In 2003, a pilot study by Su and colleagues compared 9.6 g/day n-3 LCPUFAs with placebo in 28 patients over 8 weeks using a randomised, double-blind design. All but one patient was medicated and remained on their medication throughout the trial. The group receiving n-3 PUFAs had significant reductions in their depression rating from the fourth week of treatment.

A 2005 study involved 77 depressed patients randomly assigned to receive either 8 g/day of DHA-enriched (1.23%) fish oil or olive oil, in addition to existing medication, over 12 weeks. Interestingly, the fish oil group did not show significant improvement over the olive oil group, but both groups improved in mood over baseline. This was significant at 2 weeks and remained so throughout the study (Silvers et al 2006). Similarly, an Australian study of 83 outpatients taking antidepressant medication, administered 2.2 g/day DHA and 0.6 g/day EPA over 4 months found no demonstrable benefit compared with those taking an olive oil placebo (Grenyer et al 2007). The use of olive oil placebos in both of these trials has been speculated as being a confounding variable.

A randomised study conducted in 28 children aged 6–12 years and diagnosed with depression using the Children's Depression Rating Scale (CDRS), Children's Depression Inventory (CDI) and Clinical Global Impression (CGI) found symptomatic improvement following 1 month of treatment with omega-3 fatty acids (Nemets et al 2006).

Bipolar disorder

In spite of a growing number of studies investigating fish oils in the treatment of this condition, data from these are plagued by methodological weaknesses, as evidenced by a recent Cochrane review which included only one study, Frangou et al (2006), following exclusion of 23 other trials for various reasons (Montgomery & Richardson 2008). Studies have employed either mixed EPA/DHA preparations or pure ethyl-EPA delivering a minimum of 1 g/day typically in combination with standard pharmaceuticals. A number of studies point towards improvement of depressive symptoms, with no evidence of benefit during manic phases.

Aggressive and impulsive behaviour

Animal studies demonstrate increased aggression test scores in rats and other species deprived of n-3 LCPUFAs either during gestation or early life which has been linked to deficits in neuronal arborisation and multiple indices of synaptic pathology, including deficits in serotonin and mesocorticolimbic dopamine neurotransmission (Hibbeln et al 2006, Liu & Raine 2006). Human data also support this proposition, whereby preterm delivery is associated with deficits in fetal cortical DHA accrual, and children/adolescents born preterm exhibit deficits in cortical grey matter maturation, neurocognitive deficits particularly in the realm of attention, impulsivity and increased risk of ADHD and schizophrenia (Hibbeln et al 2006, McNamara & Carlson 2006). While there is strong support for the biological basis for a relationship between n-3 LCPUFAs and aggressive and impulsive behaviour (Garland & Hallahan

2006), the results of interventional studies have been somewhat mixed.

DHA has been used to reduce aggressive behaviour in children and adolescents. One placebo-controlled study of 42 college students showed that DHA supplementation (1.5–1.8 g/day) prevented an increase in aggression towards others at times of mental stress (Hamazaki et al 1996); however, had no effect on aggressive behaviour under non-stressful conditions (Hamazaki et al 1998). A 2005 randomised, placebo-controlled clinical trial in 166 Japanese children aged 9–12 years administered 3.6 g DHA and 840 mg per week via both supplements and fortified foods over a period of 3 months (Itomura et al 2005). While reducing aggression in girls, concomitant with improved EPA:AA RBC ratios, the same effect was not evident in boys. Impulsivity amongst female subjects was also significantly reduced in the treatment group.

A recent interesting study examined the use of n-3 LCPUFAs in polysubstance abusers (Buydens-Branchey et al 2008). The intervention was 2.25 g EPA, 500 mg DHA administered over 3 months to 24 individuals and resulted in decreased anger and anxiety scores, corresponding with plasma increases in both EPA and DHA. Clinical studies also suggest that n-3 LCPUFA supplementation can improve the impulsivity/aggressivity dimension of borderline personality disorder (Diaz-Marsa et al 2008). However, in individuals exhibiting recurrent self-harm, scores for impulsivity, aggression and hostility remained unchanged, in spite of decreased depression and suicidality scores, when treated with 1.2 g EPA and 900 mg DHA per day over 12 weeks (Hallahan et al 2007).

Attention-deficit hyperactivity disorder

It has been reported that many children with ADHD have EFA deficiency (mainly n-3 FA) with a high correlation between severity of symptoms and severity of deficiency (Yehuda et al 2005). Deficiency may be due to insufficient dietary intake or inefficient conversion of EFA to LCPUFAs. Several studies have investigated the effects of supplemental fatty acids in ADHD with mixed results; however, interpretation of findings is difficult because of the use of different treatments, measurements and subject selection (Richardson & Puri 2000).

Schizophrenia

Schizophrenic patients have been frequently found to have low LCPUFAs (Peet 2003, 2006). A new study adds to this, demonstrating high saturated and monounsaturated fat in red cells at the expense of LCPUFAs of both the 3 and 6 families (Kemperman et al 2006). A key researcher in the area of EFAs and psychiatry also points to the significant overlap between core features of the metabolic syndrome and established physiological aberrations evident in schizophrenia, including visceral adiposity, insulin resistance, dyslipidaemias, increased inflammatory markers and reduced n-3 LCPUFAs in cell membranes (Peet 2006). Importantly, these similarities pre-date the introduction of the novel antipsychotics, which are known to be diabesogenic. Schizophrenic patients demonstrate a 2–4-fold increased risk of type 2 diabetes mellitus (T2DM) and 2–3-times greater risk of coronary artery disease mortality, which cannot be entirely related to secondary lifestyle behaviours.

According to a 2003 review, four out of five placebo-controlled, double-blind trials of EPA in the treatment of schizophrenia have produced positive results with a typical effective dose of 2 g/day of EPA for minimum of 3 months (Peet 2003). An updated Cochrane review of six studies, involving 353 subjects, has similarly concluded that ethyl-EPA may exert positive effects; however, more large well-designed, conducted and reported studies are needed (Joy et al 2006).

Cancer

It is well established that dietary fat has an influence on human cancer development and progression. Several forms of research implicate n-6 PUFAs as catalysts, whereas n-3 LCPUFAs have the opposite effect and have been shown to inhibit development and progression (Leitzmann et al 2004, Weisburger 1997). Therefore, it is the ratio of n-3 to n-6 PUFAs intake that appears to be an important factor influencing cancer incidence and progression.

This observation is supported by both animal and epidemiological studies. The largest to date involved 24 European countries and identified a significant inverse correlation with fish and fish oil consumption, when expressed as a proportion of total or animal fat, for both male and female colorectal cancer and for female breast cancer (Caygill et al 1996). Importantly, the protective effects were only detected in countries with a high animal fat intake, suggesting that fish oil protects against the promotional effects of animal fat in carcinogenesis.

Breast and prostate cancers

A 2003 review found that overall it remains unclear as to whether dietary fish or fish oil consumption exerts a protective effect against the development of breast and prostate cancers (Terry et al 2003). The assessment of EPA and DHA intake and their relation to n-6 fatty acid intake and cancer incidence still requires further examination before conclusions can be confidently made. An updated review conducted by the same researchers in 2004 (Terry et al 2004) reached a similar conclusion; however, they also observed that those studies that assess omega-3 intake concomitant with the omega-6 consumption were most likely to yield a statistically significant inverse relationship between fish oils and breast and prostate cancers. Once again this reinforces the understanding that the fats due to interrelated metabolism and actions should not be viewed independently.

A prospective cohort study in the USA of 47,866 men aged 40–75 years with no cancer history were assessed using a 131-item semiquantitative food-frequency questionnaire administered annually over 14 years, as part of the Health Professionals Follow-Up study. Nutrient intake data from this trial suggests an association between

ALA and advanced prostate cancer, but an inverse relationship with the ALA metabolites, EPA and DHA. Earlier studies investigating the relationship between ALA and prostate cancer have had mixed results while the inverse relationship with EPA/DHA appears to be largely supported. Again the authors demonstrate that ratios of omega 3:6 appear to be highly influential in conveyed risk (Leitzmann 2004).

Colorectal cancer

Epidemiological evidence investigating associations between fish intake and colorectal cancer have produced mixed findings (Caygill et al 1996, Daniel et al 2009), with the most recent prospective cohort study (Cancer Prevention Study-II Nutrition Cohort) involving over 99,000 individuals failing to demonstrate a protective effect of increased n-3 intake. In fact, increased consumption of ALA was associated with increased risk in women. Contrastingly, higher marine n-3 intake did appear protective. The latter finding is consistent with the results of other large prospective studies on this issue (Hall et al 2008).

Other sources of evidence attribute both EPA and DHA and their main dietary source, fish oil, with antineoplastic effects in colorectal cancer (Llor et al 2003). Fish oil supplementation, in one study, providing 4.1 g EPA and 3.6 g DHA per day in patients with sporadic adenomatous colorectal polyps was reported to reduce the percentage of cells in the S-phase in the upper crypt of the rectal mucosa (Anti et al 1992). The evidence to date as reviewed in 2004 by Roynette et al suggests a primary preventative effect with some residual ambiguity over the safety of n-3 LCPUFAs with respect to secondary tumour formation.

One study has investigated the effects of n-3 LCPUFA parenteral supplementation postoperatively on clinical outcomes and immunomodulation in colorectal cancer patients using a randomised, double-blind design (Liang et al 2008). Treatment effect comparisons revealed that those treated with n-3 LCPUFAs had significantly lower serum IL-, TNF-alpha and increased ratios of CD^{4+}/CD^{8+}. These patients also tended towards shorter postoperative hospital stays. Consequently, the authors conclude that such a treatment regime may have beneficial effects on lowering the magnitude of inflammatory responses and modulating the immune response in this patient group.

The results of a recent in vitro study have demonstrated synergistic inhibition of proliferating colon cancer cells using a combination of lycopene and EPA (Tang et al 2008). The results of other in vitro studies attribute the protective effects of n-3 LCPUFAs with DHA rather than EPA (Kato et al 2007). Both animal studies and RCTs are now required to clarify the 'active' fatty acid and confirm these findings.

Diabetes

Increasing the intake of n-3 LCPUFAs has been shown to be both preventative in a healthy population and beneficial in people with diabetes (Montori et al 2000, Nettleton & Katz 2005, Sirtori & Galli 2002, Sirtori et al 1997). Although there have been random reports of improved glucose control with fish oil supplementation, a review published in 2004 cites two large meta-analyses of trials with n-3 LCPUFAs in subjects with diabetes, which found no adverse or positive effect on glucose control or impact on glycated haemoglobin, with a recent Cochrane review making the same conclusion (Hartweg et al 2008).

Two meta-analyses found that fish oil supplementation lowers plasma TG levels in type 2 diabetic subjects; however, a possible rise in plasma LDL cholesterol may occur (Balk et al 2006, Montori et al 2000). The latter has been speculated, to be the result of enhanced conversion of VLDLs and studies in primates suggest that n-3 LCPUFA enriched LDLs do not convey the same atherogenic potential (Jung et al 2008). Additionally, no significant effect occurs on glycaemic control, total cholesterol or HDL cholesterol. In addition to this, more recent studies reveal an average of 7.4% increase in HDL levels concomitant with a 25% reduction in TGs in response to 203 g of EPA/DHA supplementation over 6 months (Sirtori et al 1998). Such findings are supported by the results of other trials in diabetics (Nettleton & Katz 2005).

Despite the potential benefits associated with n-3 LCPUFAs, a 2008 Cochrane review of 23 RCTs involving 1075 individuals concluded there is currently insufficient evidence to recommend high-dose fish oils to T2DM patients for cardiovascular benefits (Hartweg et al 2008).

Weight reduction

In addition to attenuating negative PUFA changes associated with weight loss regimes (Hlavaty et al 2008) and improving insulin resistance in overweight subjects (Ramel et al 2008), there is limited evidence that n-3 LCPUFAs may be associated with reduced incidence of obesity, ease of weight loss and maintenance of body weight in this population (Nettelton & Katz 2005). A recent study found that overweight and obese subjects consuming >1300 mg/day n-3 LCPUFAs compared with those consuming <240 mg/day demonstrated significantly increased satiety 2 hours post-prandially, which correlated with an increased omega 3:6 (Parra et al 2008).

Inflammatory diseases

Numerous clinical trials have investigated the effects of fish oil supplementation in several inflammatory and autoimmune diseases, such as rheumatoid arthritis, Crohn's disease, ulcerative colitis, lupus erythematosus and migraine headaches (Belluzzi 2002, Belluzzi et al 1996, Miura et al 1998, Simopoulos 2002). Although not all trials have produced positive results, many of the placebo-controlled trials reveal significant benefit in chronic disease, including decreased disease activity and sometimes reduced requirement for anti-inflammatory medicines (Adam et al 2003).

Rheumatoid arthritis (AR)

Of the inflammatory diseases, the use of fish oil supplementation is most widely seen and supported in RA. According to multiple randomised, controlled studies, fish oil supplements have been consistently shown to reduce symptoms in RA, such as the number of tender joints, pain intensity and morning stiffness (Adam et al 2003, Cleland et al 2003, Goldberg & Katz 2007, Kremer 2000, Ulbricht & Basch 2005, Volker et al 2000). Generally, supplements are taken daily as adjuncts to standard therapy with clinical effects appearing after 12 weeks. A dose ranging from 30 mg to 40 mg/kg of EPA and DHA daily has been used successfully, although some studies have found a minimum of 3 g/day is required. Results from a double-blind, crossover study suggest that the beneficial effects obtained from fish oil capsules are further enhanced when combined with an anti-inflammatory diet providing less than 90 mg/day of AA (Adam et al 2003).

Symptomatic relief with n-3 LCPUFAs in RA was more recently confirmed in a meta-analysis of 17 randomised controlled trials assessing the pain relieving effects in RA patients or joint pain secondary to inflammatory bowel disease and dysmenorrhoea (Goldberg & Katz 2007). Supplementation for 3–4 months significantly reduced patient-reported joint pain intensity, minutes of morning stiffness, number of painful and/or tender joints and non-steroidal anti-inflammatory drug (NSAID) consumption. Significant effects were not detected, however, for physician assessed pain or Ritchie articular index. These papers, together with other authoritative reviews, conclude that based on high-level evidence, n-3 LCPUFAs are an attractive adjunctive treatment for joint pain associated with rheumatoid arthritis and have a beneficial follow-on effect on cardiovascular morbidity and mortality pertinent to this population (Proudman et al 2008).

Although the anti-inflammatory activity of fish oil supplementation is thought to be chiefly responsible for symptom relieving effects, there is also evidence that n-3 LCPUFAs can modulate expression and activity of degradative factors that cause cartilage destruction (Curtis et al 2000). A 2005 randomised study found that fish oil supplements (3 g/day), whether taken alone or in combination with olive oil (9.6 mL), produced a statistically significant improvement ($P < 0.05$) compared to placebo on several clinical parameters (Berbert et al 2005). Significant improvements were observed for joint pain intensity, right and left handgrip strength after 12 and 24 weeks, duration of morning stiffness, onset of fatigue, Ritchie's articular index for pain joints after 24 weeks, ability to bend down to pick up clothing from the floor and getting in and out of a car after 24 weeks. The group using a combination of oils showed additional improvements with respect to duration of morning stiffness after 12 weeks, patient global assessment after 12 and 24 weeks, ability to turn taps on and off after 24 weeks and rheumatoid factor after 24 weeks. In addition, this group showed a significant improvement in patient global assessment compared with fish oils alone after 12 weeks.

Based on these results, it appears that while fish oils will not improve all parameters of RA, overall they have demonstrated symptomatic relief in the majority and result in significantly reduced use of anti-inflammatory and corticosteroid use, a fact that MacLean et al (2004) acknowledge and which is confirmed by a 2005 review by Stamp et al and meta-analysis by Goldberg and Katz (2007). There appears to be little evidence of sustained improvements following cessation of the supplements.

A 2008 paper from the Joint Nutrition Society notes that, in addition to modifying the lipid mediator profile, n-3 LCPUFAs exert effects on other aspects of immunity relevant to RA, such as antigen presentation, T-cell reactivity and inflammatory cytokine production (Calder 2008).

Reducing incidence of RA

A large prospective cohort study (n = 57,053) investigating the association between dietary factors and risk of RA found that each increase in intake of 30 g fatty fish (≥8 g fat/100 g fish) per day was associated with 49% reduction in the risk of RA (P = 0.06); however, a medium intake of fatty fish (3–7 g fat/100 g fish) was associated with significantly increased risk of RA (Pedersen et al 2005). No associations were found between risk of RA and intake of a range of other dietary factors, including long-chain fatty acids, olive oil, vitamins A, E, C and D, zinc, selenium, iron and meat. The authors caution that due to the limited number of patients who developed RA during follow-up, it is not yet possible to make firm conclusions.

Asthma

Omega-3 LCPUFAs exhibit anti-inflammatory activity and epidemiological evidence has demonstrated an inverse relationship between fish intake and asthma risk and improved lung function (Wong 2005). Recent evidence suggests that this protective effect may extend back as far as adequate fetal n-3 LCPUFAs exposure (Salam et al 2005). A recent 16-year follow-up investigation of offspring born to women supplemented with 2.7 g/day fish oils from week 30 until delivery as part of a RCT confirms this proposition (Olsen et al 2008). Children born to mothers in the fish oil group demonstrated a 63% reduction in asthma diagnoses and 87% reduction in the prevalence of allergic asthma. Results such as these may help to explain the lack of protective effects associated with increased n-3 LCPUFA levels in early childhood reported in some of the literatures (Almqvist et al 2007, Marks et al 2006).

A 2002 Cochrane review of nine RCTs conducted between 1986 and 2001 concluded that n-3 LCPUFAs supplementation demonstrated no consistent effect on any of the analysable outcomes: forced expiratory volume in 1 second, peak flow rate, asthma symptoms, asthma medication use or bronchial hyper-reactivity (Woods et al 2002). However, one of the RCTs involving children showed that when fish oil supplementation was

combined with dietary changes, positive results were obtained, as evidenced by improved peak flow and reduced asthma medication use.

An interesting recent crossover study of 72 asthmatic children aged 7–10 years, involved five randomised phases of treatment each lasting 6 weeks: placebo; omega 3 (300 mg/day combined EPA and DHA); zinc (15 mg/day); vitamin C (200 mg/day); combination of all nutrients (Biltagi et al 2009). While the n-3 LCPUFA supplementation was associated with improved lung function and a reduction in both sputum production and markers of airway inflammation, these positive effects were significantly augmented when combined with zinc and vitamin C, suggesting that a more broad nutritional approach to inflammation and oxidation control results in greatest clinical outcomes.

The equivocal nature of interventional studies with n-3 LCPUFAs, as documented by a 2005 review (Wong), may be clarified in future with the identification of a subtype of asthma more likely to respond to EFA manipulation.

Another interesting paper reports on three patients with disabling salicylate intolerance producing urticaria, asthma and anaphylactic reactions who, following administration of 10 g/day fish oils for 6–8 weeks, experienced complete or virtually complete resolution of symptoms (Healy et al 2008). Treatment response was so effective corticosteroids could be discontinued, however, symptoms reappeared following fish oil dose reduction.

In recent years, the focus for fish oils in asthma has broadened to include other populations such as athletes. One randomised, double-blind, crossover study of 16 non-atopic asthmatic patients with documented exercise-induced broncoconstriction (EIB) compared the effects of 3.2 g of EPA and 2.0 g DHA per day and placebo capsules for 3 weeks. During treatment with fish oils, subjects demonstrated improved pulmonary function to below the diagnostic EIB threshold, which was associated with a concurrent reduction in bronchodilator use. Measurement of leukotriene B(4) and B(5) levels also confirmed a significant reversal of the inflammatory picture (Mickleborough et al 2006).

Atopic dermatitis and eczema

In a sample of adult patients (n = 53), randomised to 5.4 g/day DHA or isoenergetic saturated fats for 20 weeks, active fish oil treatment produced significant clinical improvements which correlated with increases in plasma DHA (Koch et al 2008); however, due to the small sample size, larger studies are required to confirm these preliminary results.

Previously, a double-blind multicentre study involving 145 patients with moderate to severe atopic dermatitis showed that n-3 LCPUFAs (6 g/day) improved clinical symptom scores by 30% after 4 months' treatment (Soyland et al 1994). The results were confirmed by patients' subjective scoring. An earlier, 12-week, prospective, double-blind study produced similar results with a dose of 10 g/day (fish oil) improving overall severity of atopic dermatitis and reducing scaling (Bjorneboe et al 1989).

Clinical note — The 'new' fish oils?

Pressing issues of non-sustainability of both wild harvesting and aquaculture together with increasing contaminants in both fish and their products would have stimulated researchers to search for alternative sources to meet our increasing omega-3 demand (Racine & Deckelbaum 2007, Robert 2006). One burgeoning interest is algal sources of EPA/DHA, which may offer a genuine alternative as either supplements or fortificants (Doughman et al 2007, Kris-Etherton & Hill 2008, Racine & Deckelbaum 2007). Microalgae, such as *Crypthecodinium cohnii* and *Schizochytrium* spp., represent part of the coastal food chain as a primary food source for shellfish, contain naturally high levels of DHA, no contaminants (Arterburn et al 2000, Doughman et al 2007) and are currently commercially developed as sustainable crops (Doughman et al 2007, Whelan & Rust 2006). Initial human studies have confirmed both bioequivalence and comparable clinical efficacy with other DHA sources such as salmon (Arterburn et al 2000, Doughman et al 2007). Algal oils also have good safety profiles, as evidenced by approval of select species by the FDA (Whelan & Rust 2006). While this appears promising, a number of limitations regarding microalgal omega-3 sources have already been identified, including low EPA content, absence of other nutrients found in fish (e.g. protein), possible inhibition of elongases and desaturases secondary to high DHA intake and minor risk of allergenicity (Doughman et al 2007, Kris-Etherton & Hill 2008).

Reducing incidence of eczema

The results of a recent, prospective, longitudinal study from Sweden of 4921 infants' diets, exposure patterns and eczema diagnoses have found a protective effect for early introduction of fish (Alm et al 2009). Infants introduced fish prior to 9 months of age demonstrate reduced rates of eczema at 1 year (OR 0.76). This finding flies in the face of previous primary prevention strategies whereby many child health authorities have encouraged delaying the introduction of fish in order to reduce allergy.

OTHER USES

Fish oil supplements are also used in the management of acute respiratory distress syndrome, psoriasis, multiple sclerosis, osteoporosis and dysmenorrhoea and in children with dyslexia.

DOSAGE RANGE

- Fish should be considered part of a healthy diet for everybody and be consumed at least twice a week. Care should be taken to avoid intake of fish known or suspected to contain higher levels of mercury.
- Additional administration of n-3 LCPUFA supplements should be considered in specific groups.

- Fish meals should consist of deep sea oily fish, whereas fried or processed fish containing partially hydrogenated fats and salted or pickled fish should be avoided.

Cardiovascular disease

Secondary prevention trials after MI indicate that consumption of 0.5–1.8 g/day of EPA and DHA from fish or fish oil supplements may be beneficial. Intake of marine-derived omega-3 fatty acids can be increased through diet or with fish oil supplements.

- An expert US panel of nutrition scientists has recommended an intake of 0.65 g/day, whereas the British Nutrition Foundation's recommendation is 1.2 g/day (Din et al 2004).
- National Heart Foundation/Cardiac Society of Australia and New Zealand: >2 serves/wk.
- Patients who have experienced coronary artery bypass surgery with venous grafts: 4 g/day of n-3 LCPUFAs.
- Moderate hypertension: 4 g/day of fish oils.
- Elevated TG levels: 1–4.6 g/day of fish oils.

Other conditions

- Aggression induced by mental stress: DHA supplementation, 1.5–1.8 g/day.
- Anger and anxiety reduction in polysubstance abuse withdrawers: 2.25 g EPA, 500 mg DHA and 250 mg other omega-3 per day.
- Asthma prevention in pregnancy: 2.7 g/day from week 20 gestation until delivery.
- Asthma treatment in children: 300 mg combined EPA & DHA with 15 mg zinc and 200 mg vitamin C per day.
- Atopic dermatitis: 6 g/day fish oils or 5.4 g/day DHA.
- Autism: 5 g/day.
- Bipolar disorder: 1 g/day EPA.
- Colorectal cancer: 4.1 g EPA + 3.6 g DHA daily.
- Dementia: DHA supplementation, 4.32 g/day.
- Depression: 1 g/day EPA or 9.6 g/day fish oils.
- Exercise-induced asthma in non-atopic individuals: 3.2 g EPA + 2.0 g DHA daily.
- High blood pressure: 3–5.6 g/day.
- Intermittent claudication: 1.8 g EPA and 1.2 g DHA per day.
- Pregnancy: According to the WHO and FAO, the pregnant woman should take at least 2.6 g of n-3 EFAs, incorporating 100–300 mg of DHA daily to look after the needs of the fetus.
- Rheumatoid arthritis: 30–40 mg/kg body weight of EPA and DHA daily.
- Schizophrenia: 2 g/day EPA.
- Weight reduction and improved insulin sensitivity: 660 mg EPA and 440 mg DHA/day.

ADVERSE REACTIONS

Fish oil supplementation is generally safe and well tolerated. The few side effects reported are usually mild and can include gastrointestinal discomfort and loose bowels, halitosis and a fishy odour of the skin and urine.

SIGNIFICANT INTERACTIONS

Antiplatelet agents

Theoretically, concomitant use with antiplatelet agents may increase the risk of bleeding; however, multiple clinical studies have found no clinically significant effect on bleeding and one study has suggested that the combined effects may be beneficial (Engstrom et al 2001) — no clinically significant interaction expected at therapeutic doses.

Anticoagulants

Clinical studies of surgical patients taking warfarin have not found a clinically significant increase in bleeding. According to one clinical study, bleeding time is increased at very high doses of 12 g/day. Usual therapeutic doses, which tend to fall below this dosage, appear safe in this population although care should still be taken. Very high doses >12 g should be used only under professional supervision to ensure no adverse outcomes.

NSAIDs

Additional anti-inflammatory effects are theoretically possible with concurrent use of fish oil supplements, suggesting a beneficial interaction. Drug dosage may require modification.

Pravastatin

Low-dose pravastatin combined with fish oil supplementation is more effective than pravastatin alone for changing the lipid profile after renal transplantation, according to one clinical study — potential beneficial interaction.

CONTRAINDICATIONS AND PRECAUTIONS

One area of concern is the growing problem of heavy metal contamination found in fish, specifically mercury. In areas where contamination is possible, fish oil supplements may represent a safer option. According to the *Australia New Zealand Food Standards Code*, fish with higher levels of mercury include: swordfish, southern bluefin tuna, barramundi, ling, orange roughy, rays and shark. Fish considered to have lower levels of mercury include: mackerel, silver wahoo, Atlantic salmon, canned salmon and canned tuna in oil, herrings and sardines.

People with bleeding disorders should take fish oil supplements under medical supervision.

PREGNANCY USE

Fish oils appear to be safe during pregnancy at dietary doses and is likely to have benefits.

PATIENTS' FAQs

What will this supplement do for me?

Regular consumption of fish oils may reduce total mortality, cardiovascular mortality and morbidity, dementia and depression. Additionally, beneficial effects have been demonstrated in a wide variety of conditions.

When will it start to work?

This will depend on the dosage taken and indication for use.

Are there any safety issues?
People with bleeding disorders should take fish oil supplements under medical supervision.

PRACTICE POINTS/PATIENT COUNSELLING

- As precursors of eicosanoids, polyunsaturated fatty acids found in fish oils exert a wide influence over many important physiological processes.
- They have demonstrated anti-inflammatory, immunological, neurological, antiplatelet and chemopreventative effects, and a range of beneficial actions within the cardiovascular system.
- Daily ingestion of at least 1 g EPA and DHA (equivalent to fish eaten at least twice weekly) may result in a reduction in total mortality, cardiovascular mortality and morbidity and incidence of dementia and depression.
- Trials generally support the use of supplements in a range of inflammatory and autoimmune diseases such as rheumatoid arthritis and atopic dermatitis, elevated TGs, hypertension and other cardiovascular conditions, poor cognitive function and diabetes. Preliminary research suggests a possible role in depression.
- People with bleeding disorders should take fish oil supplements under medical supervision.

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Flaxseed oil

HISTORICAL NOTE For over 5000 years, flaxseed in its various forms has been a part of the diet of people in Asia, Africa and Europe. It has a long history of use as both a food and a medicine, with the seed being most commonly used. The oil was also popular and has been a traditional food of the Egyptians from the time of the Pharaohs to the present day. The oil is also consumed by the Chinese, who documented its medicinal properties in the Pen-T's AO, the Great Chinese Pharmacopeia (Judd 1995). Its Latin name *usitatissimum* means 'most useful', suggesting its various uses have been recognised for centuries (Kolodziejczyk & Fedec 1995). Interestingly, research into its nutritional properties and effects on human health was not studied in earnest until the 1980s (Cunnane & Thompson 1995). In Australia in 1981, cultivation of a low alpha-linolenic acid (ALA) variety, now known as Linola, was pioneered in an attempt to improve the stability of the oil and increase its commercial viability as a cooking oil. Such modifications were successful and resulted in ALA content <3.0% and a higher concentration of linoleic acid than the naturally occurring form (Bhatty 1995, Hall et al 2006). These modified oils are not used for medicinal purposes.

OTHER NAMES

Flax oil and linseed oil

Internationally, it is accepted that 'flaxseed' refers to products for human consumption, whereas 'linseed oil' refers to products that have been denatured, made unfit for human consumption, and used in commercial products, such as paints and varnishes.

BOTANICAL NAME/FAMILY

Linium usitatissimum (family Linaceae)

PLANT PART USED

Fixed oil is derived from the seeds of the plant. Due to the highly polyunsaturated nature of the oil (≈ 73%), extracts are obtained by cold-pressing rather than heat extraction. Flaxseed oil (FSO) is highly susceptible to photo-oxygenation, so it is packaged in opaque bottles. It is also susceptible to auto-oxidation, resulting in the production of hydroperoxides and aldehydes that can give a rancid flavour. Encapsulated FSO is considered more stable, particularly when antioxidants are added (Kolodziejczyk & Fedec 1995).

Eating the seeds versus taking the oil

With the rash of flaxseed-based bakery goods that have arrived on the market in recent years, it is valuable to review the bioavailability and therapeutic potential of such products. A recent study compared the effect of consuming flaxseeds (30 g/day) versus both milled flaxseed (30 g/day) and FSO (6 g/day) over a 3-month period on corresponding blood lipid profiles (Austria et al 2008). These results reveal that while the milled preparation and oil extract produced significant physiological increases in ALA levels (with the FSO producing the largest effect), consumption of the whole seeds did not (Austria et al 2008). Effects in individuals consuming the whole seeds also demonstrated the greatest inter-individual variability, probably related to the degree of chewing each subject performed. Consequently, while the consumption of whole flaxseeds can boost dietary fibre and phytoestrogen content, they do not appear to be a reliable means to supplying ALA.

CHEMICAL COMPONENTS

Flaxseed oil contains several types of fatty acids (FAs). It contains a high concentration of ALA, ranging from 40% to 60%, and is the most concentrated plant source of omega-3 FA identified to date.

FSO also contains unsaturated FAs, such as linolenic acid, linoleic acid and oleic acid. Linoleic acid (LA or C18:2 n-6) and oleic acid each contribute 15% to the total FA content of the oil. Due to the range of FA present, it contains precursors for the

Clinical note — Is FSO equivalent to the fish oils?

FSO has been commercially promoted as the vegetarian or vegan alternative to fish oils, with many of the health benefits ascribed to fish oils also being attributed to the oil. A review of the literature suggests that FSO is unlikely to be equipotent with fish oils in the treatment of a variety of conditions.

The ALA present in FSO can theoretically undergo desaturation and elongation to synthesise eicosapentanoic acid (EPA) and docosahexaenoic (DHA), which are found in fish oil; however, most studies using oral FSO intake demonstrate only moderate increases in EPA and DHA remains unchanged (Allman et al 1995, Arterburn et al 2006, Barcelo-Coblijn et al 2008, Kelley et al 1993, Mantzioris et al 1994, Nestel et al 1997). Although results from one early study suggest that increases in DHA levels may be achieved with long-term supplementation (Cunnane et al 1993), more recent studies fail to confirm this result (Barcelo-Coblijn et al 2008, Harper et al 2006, Hussein et al 2005).

Conversion rates of ALA to EPA and docosapentaenoic acid (DPA) are reported to be < 10% (Harris et al 1997) and approximately 8%, respectively, whereas the DHA yield ranges from 0% to 0.5%. One explanation for this is that DHA synthesis is under separate regulatory control, a hypothesis supported by enzymatic studies (Burdge 2004). Theoretically, therefore, a 20 mL serve of FSO, providing 11.1 g of ALA, would result in a maximum of 880 mg DPA and 5 mg of DHA. A recent study investigating optimal minimal dosing of FSO, however, reported that increased red blood cell omega-3 concentrations are evident at a minimum of 2.4 g/day taken over 2 weeks, with the largest effect seen at the 6–8-week timeframe (Barcelo-Coblijn et al 2008). These authors also report that 1.2 g/day of fish oil produced comparable changes, concluding that FSO or other plant-based ALA sources represent a realistic alternative source of omega-3s and at doses much lower than previously studied.

However, there is marked inter-individual variation in conversion efficacy, even in the face of comparable background diets and some notable gender differences, with resultant DHA typically undetectable in males consuming high-dose ALA (Arterburn et al 2006). Adding to this puzzle is a wide range of other variables that can inhibit the conversion of ALA into its metabolites. For instance, high dietary intake of linoleic acid (LA), common in Western cultures (Arterburn et al 2006, Breslow 2006), inhibits both the uptake of ALA and its conversion to long-chain metabolites due to competition for shared enzymes. An interesting study conducted in 1998, which used radioactively labelled ALA, showed that a diet high in omega-6 fats reduced conversion by 40–50% (Gerster 1998), resulting in 70% net reduction of long chain omega-3 end products (Arterburn et al 2006). This adds weight to the argument that the ratios of FAs may have the primary influence on their resultant health benefits. The authors of this study suggest that the ratio of omega-6:omega-3 should not exceed 4. In contrast, the typical American diet demonstrates an LA:ALA ratio of ≥11.5 (Arterburn et al 2006, Breslow 2006). However, there are authors who refute that the ratios are a major determinant (Goyens et al 2006).

Other studies have reported abnormal or compromised activity of the delta-6 and delta-5 desaturase enzymes in the elderly, diabetics and patients with a variety of metabolic disorders, as well as those individuals with increased dietary intake of saturated fats, *trans*-fatty acids and alcohol (David & Kris-Etherton 2003). Studies using radioisotopes of ALA have revealed significant gender differences in conversion capability, with women demonstrating higher levels of FA metabolites. It is believed that this is due to their higher oestrogen levels, a theory supported by the increased conversion capacity evident in women taking synthetic oestrogens and speculated as representing a physiological adaptation that ensures adequate essential fatty acid (EFA) delivery to the fetus in pregnancy (Burdge 2004).

Finally, it appears that ALA conversion to long chain omega-3 FA is also self-limiting, with high intakes producing significantly increased oxidation and impairing conversion into EPA and DHA (Arterburn et al 2006, Schwab et al 2006). Based on the available evidence, it appears that ALA conversion is relatively inefficient in humans, making ALA a poor means of increasing omega-3 levels (Arterburn et al 2006).

omega-3, -6 and -9 families. Environmental factors can profoundly influence the unsaturated FA composition and ratios (Hall et al 2006). FSO may also contain varying amounts of the lignan, secoisolariciresinol diglycoside (SDG), which is a precursor to enterodiol and enterolactone.

Flax seeds contain 41% fat, 28% dietary fibre, 21% protein and significantly higher amounts of lignans, which behave as phyto-oestrogens (Morris 2001). This review, however, focuses on FSO.

MAIN ACTIONS

The main actions of FSO have been attributed to its high ALA content. ALA is subject to three different metabolic fates: (a) incorporation into structural, transport or storage pools, (b) beta-oxidation as an energy source and (c) elongation and further desaturation to form EPA, DPA and DHA. It appears that all three contribute to the biological effects of this oil.

ALA's direct role in cell membrane structure is likely to be minor, with ALA representing less than 0.5% of the total FA in cell membranes and blood lipids in healthy adults and possessing a limited distribution (e.g. adipose, rectal epithelium, cheek, heart) (Arterburn et al 2006). However, its limited propensity to generate the n-3 metabolites, EPA and DHA, the major FAs in cell membranes, could represent an indirect effect via this mechanism (Burdge 2004).

Studies exploring the metabolism of ALA have revealed that 22% of ALA undergoes beta-oxidation in women and 33% in men. Once broken down the carbon chain can be used as fuel or in the synthesis of cholesterol and other fatty acids such as palmitic, palmitoleic, stearic and oleic acids de novo (Burdge 2004). FSO also influences the eicosanoid production cascade via conversion of the n-3 and n-6 parent FAs in FSO to their respective metabolites.

It is also thought that some of the actions of FSO may be independent of its FA content and can be attributed to the lignan SDG. This has been partly supported by research conducted by Prasad et al in 1998 and again in 1999.

Anti-inflammatory

Metabolites of ALA and LA act as substrates for the formation of the anti-inflammatory eicosanoids, comprising prostaglandins, thromboxanes and leukotrienes (Gerster 1998). ALA suppresses AA production by interfering with the conversion of LA to AA, and reduces the biosynthesis of inflammatory eicosanoids, although not to the same extent as EPA and DHA (Morris 2001). Cytokines, another important group of inflammatory mediators, are generated in response to these eicosanoids and are influenced by changes in the n-3:n-6 ratios in cell membranes (James et al 2000). In one study, ingestion of FSO (equivalent to 13.7 g/day ALA) for 4 weeks by healthy male subjects resulted in a 30% reduction in TNF-alpha, 31% reduction in IL-1-beta, 29% reduction in eicosanoids thromboxane B(2) and 30% reduction in PGE_2 (Caughey et al 1996). In contrast, more recent studies have failed to demonstrate anti-inflammatory effects (Barcelo-Coblijn et al 2008, Paschos et al 2007).

In animal models, ALA has consistently demonstrated eicosanoid-mediated anti-inflammatory effects; however, the magnitude of the effect has been dependent on the levels of both ALA and LA in the diet, duration of use and type of tissue studied (Cunnane & Thompson 1995).

Immune effects

Evidence of ALA deficiency has been reported in patients on prolonged total parenteral nutrition (TPN), which resulted in reduced T-helper cells to below the normal range and impaired proliferation of peripheral blood mononuclear cells. Although supplementation with small doses of ALA corrected these abnormalities, the effect of ALA on human immune cells appears to be paradoxical, with evidence of immune function inhibition at higher doses (≥40 mL/day FSO) (Kelley 1992).

Cardiovascular effects

Because ALA can be converted to long-chain (n-3) PUFA in humans and may potentially reproduce the beneficial effects of fish oils, FSO and ALA have been studied as possible preventive or treatment agents for cardiovascular disease. Epidemiological evidence of secondary coronary event prevention from ALA, in the context of a modified Mediterranean diet, support this premise (Schwab et al 2006). While numerous studies have suggested that FSO and ALA exert a myriad of different mechanisms in the body, which can be beneficial in cardiovascular disease, inconsistent results have meant that much is still unknown and more research is required.

Antithrombotic and antiplatelet activities

The question of whether supplementation with ALA affects platelet aggregation remains unclear. A major determinant appears to be the degree of conversion to EPA (Garg et al 1989). When there is an increase in total EPA and reduced AA, due to ALA inhibition of LA conversion, the result is EPA replacing AA in the cell membrane and a decrease in thromboxane synthesis. In addition, SDG, another component of FSO, is metabolised to enterolactone and enterodiol and these substances may have antiplatelet-activating factor activity. Due to the variable lignan content of FSO, it is difficult to determine the clinical significance of this (Prasad 1999). Studies assessing the actual anti-aggregatory effect of FSO in humans have produced mixed results.

Reduced endothelial inflammation

A number of studies have confirmed that consumption of high-dose FSO reduces endothelium inflammation. One study assessing the cardiovascular effects of a diet in which 6.5% of total kilocalorie intake was contributed by ALA and compared with the Standard American Diet (SAD) showed that the ALA-enriched diet produced a 75% reduction in C-reactive protein, a 19% reduction in cellular adhesion molecule and a 15.6% reduction in vascular cellular adhesion molecule (VCAM) (Zhao et al 2004). An earlier study had reported these findings, demonstrating a 28% reduction in VCAM with additional reductions in soluble E-selectin (17%) (Thies et al 2001).

Lipid-lowering effect

Whole flaxseed is the form most commonly investigated in lipid-lowering studies, because the high fibre content and ALA have been speculated to act synergistically, therefore there are relatively few studies using FSO. Those that have been conducted with FSO have produced conflicting results with an almost 50/50 weighting of research showing no effect (Austria et al 2008, Kaul et al 2008, Harper et al 2006, Schwab et al 2006) or a positive one. At worst, FSO has produced increased fasting triacylglycerol concentrations and lower HDL cholesterol (Bemelmans et al 2002, Finnegan et al 2003, Wilkinson et al 2005). At best, it has been described in earlier studies as having comparable effects with bioequivalent doses of fish oils (Harris 1997, Singer et al 1986). The reality probably lies somewhere in between; however, further investigation is required. The results of a small study of 57 men by Wilkinson et al (2005), who substituted 45 g of fat per day with 15 g/day ALA derived from FSO over 12 weeks, adds to the puzzle. While confirming the mixed cardiovascular effects noted above, this treatment group also demonstrated a reduction of total cholesterol by 12.3% in comparison to a

reduction of 7.3% in the group receiving equivalent LA. While another study comparing the effects of an ALA-rich (6.8 g/day) versus EPA/DHA-rich (1.6 g/day) diet in mildly hypercholesterolaemic elderly subjects over 6 weeks revealed improved lipid responses in the ALA than the EPA/DHA group (Goyens & Mensink 2006).

The same equivocal trend is evident from studies assessing the effects of FSO on lipoproteins. Zhao's trial (2004) using an ALA-enriched diet produced a reduction in apolipoproteins A1 and B, the latter by almost 10%, however, more recent studies administering 3 g+/day of ALA from FSO over 6–26 weeks failed to demonstrate any effect on lipoprotein particle or size concentrations (Goyens & Mensink 2006, Harper et al 2006b). In spite of these seemingly disappointing findings, some researchers note that preventative effect against cardiovascular morbidity associated with increased ALA consumption in the substantial Lyon diet study, was not accompanied by cholesterol changes and therefore may point to an alternative mechanism (Kaul et al 2008).

Antiarrhythmic

Three recent studies have identified an antiarrhythmic effect mediated by ALA (Albert et al 2005, Ander et al 2004, Christensen et al 2005), although one meta-analysis concluded otherwise (Matthan et al 2005). Although the majority of research has been conducted in animals, one of the most interesting human trials involved 106 women with a mean age of 59.5 years referred for coronary angiography due to suspected coronary artery disease. Following adipose sampling for ALA levels and monitoring of 24-hour heart rate variability (HRV), it was concluded that a positive and independent association was present between ALA in adipose tissue and HRV, which was even stronger in smokers (Christensen et al 2005).

Antiatherogenic

Earlier positive findings and recent promising epidemiological data have been substantially challenged by RCTs of FSO in atherosclerosis. Following earlier positive outcomes in cardiovascular disease trials with whole flaxseed, a 1999 study showed that a low-ALA variety could produce comparable results with the earlier trials, suggesting that the antiatherogenic properties of flaxseed are independent of its ALA content (Prasad 1999).

More recent large-scale epidemiological studies continue to suggest a relationship between higher ALA intake and reduced coronary artery calcification (Djousse et al 2005); however, there is ongoing criticism that important variables have not been sufficiently accounted for, such as corresponding reductions in *trans*-FAs (Harris 2005, Wilkinson et al 2005).

Antiproliferative

ALA has demonstrated the capacity to inhibit tumour progression in animal models of mammary tumour (Chen et al 2002, Cognault et al 2000); however, the clinical significance of these findings needs to be examined further. An immunostimulant action, which is both eicosanoid and non-eicosanoid mediated, has been suggested as one possible mechanism of action. Another theory suggests that through ALA's competitive inhibition of LA, tumour cells may not receive sufficient LA, which would inhibit further cell growth (Johnston 1995). It is interesting to observe that higher dietary ALA intake is associated with a reduction in cancer deaths; however, this is not seen with higher EPA/DHA intakes, suggesting that the protective effect is not reliant on the conversion of ALA to EPA/DHA (Cunnane 1995). In addition, results from epidemiological studies show an association between low ALA consumption in humans and increased cancer deaths in general (Dolecek 1992).

Animal studies testing SDG and its metabolites from the seeds have produced promising results and suggest that they may act as selective oestrogen receptor modulating agents and therefore play a protective role against oestrogen-dependent cancers (Kitts et al 1999, Wang et al 2005).

Hypotensive

The mechanism for ALA's potential hypotensive action remains to be elucidated and in light of the bulk of negative findings, more researches to support these current results are necessary (Paschos et al 2007).

Insulin sensitising

Preliminary animal studies suggested a protective role for ALA against the development of insulin resistance and an ability to counter the associated oxidative stress (Ghafoorunissa & Natarajan 2005, Suresh & Das 2003). However, a series of clinical trials examining high-dose FSO in patients with type 2 diabetes failed to demonstrate any positive effect on glycaemic control (Barre et al 2008, Schwab et al 2006).

CLINICAL USE

Reduced mortality in coronary heart disease

The most likely mechanism by which ALA may prevent coronary heart disease (CHD) mortality is by reducing cardiac arrhythmia. In Western populations, almost 50% of all deaths from cardiovascular disease can be attributed to sudden cardiac death and the majority of sudden deaths are directly caused by acute ventricular arrhythmia (Brouwer et al 2004). A review in 2001 (Lanzmann-Petithory 2001) and a meta-analysis of three studies in 2004 (Brouwer et al) both found in favour of a protective effect from increased ALA consumption against fatal CHD (RR 0.24). The dose associated with this trend was small; only 1–3 g/day ALA higher than controls (Brouwer et al 2004). A study published in 2005, which derived data from the Nurses' Health Study (Albert et al), found that women consuming ALA in the highest two quintiles had a 38–40% lower risk of sudden cardiac death than women in the lowest quintile; however, the protective effect did not extend to other fatal forms of CHD or non-fatal myocardial infarction.

Much criticism has been directed at those researchers wanting to extrapolate prescriptive advice from these findings. An editorial by Harris (2005) notes that only one primary prevention study with ALA in CHD has been conducted and that was in the 1960s. The 1-year trial involved 13,578 Norwegian men and compared 10 g of FSO (providing 5.5/day ALA) with a sunflower seed placebo. In the analysis, there was no demonstrable difference in end points between the two groups. Recent attempts to explain this lack of effect, such as high baseline n-3 consumption by this population, appear to be well founded (Mozaffarian et al 2005).

There is an urgent need for RCTs using FSO in suitable populations to clarify the relationship between ALA and CHD mortality.

Anticlotting

There have been a surprising number of studies investigating the influence of ALA from FSO on coagulation and fibrinolysis, and enormous variation in results. Methodological issues have plagued the overall quality of evidence, with small sample sizes, inconsistent methodologies and diverse sample characteristics making interpretation difficult.

One early study compared different dietary ratios of n-6 and n-3 EFAs in relation to prostanoid production in a group of normolipidaemic men (Kelley et al 1993). The high ALA dietary intervention constituted an overall n-6:n-3 ratio of 2.7 versus control ratio of up to 27.4. Following the 18 days of the intervention, groups showed significant differences in measured outcomes, notably, that 6-keto-$PGF_{1\text{-alpha}}$ was significantly higher following the high ALA diet but no evidence of significant effect on bleeding time or thromboxane B2 production. A second study published in the same year also failed to show an effect on clotting; however, the dose of FSO used was only 4.3 g/day (Kelley et al 1993). In contrast, the results of a study using a much larger dose of 40 g/day of FSO over 23 days in 11 healthy men showed that FSO significantly reduced collagen-induced aggregation response when compared to 40 g/day sunflower seed oil (Allman et al 1995).

A follow-up study of 29 healthy males that was conducted over 6 weeks investigated the effects of a diet in which approximately 7% of the total kilocalories from polyunsaturated fat was made up of either an ALA-rich (n-3:n-6 = 1:1.2) or LA-rich diet (n-3:n-6 = 1:21). The ALA-enriched diet resulted in triple the EPA phospholipid levels compared to the LA-enriched diet, but had no demonstrable effect on coagulation or fibrinolysis, other than an increase in the ratio of activated protein C. The authors speculated that the latter finding may still prove significant, but suggest that future studies should be conducted in patients with vascular pathology, as healthy clotting profiles may have obscured the true effects of FSO (Allman-Farinelli et al 1999).

In the same year, another group of Australian researchers published the results of their study of 17 vegetarian men who were assigned to either a low- or a high-ALA diet (derived from FSO) for 28 days following a run-in baseline diet for 14 days. Again there were no significant differences in prothrombin time, activated partial thromboplastin time or plasminogen activities with the different ALA diets, despite increases in EPA and DPA levels (Li et al 1999).

Since 1994, Mutanen and Freese have conducted many studies assessing the effect of ALA and LA:ALA ratios on haemostatic factors (Freese et al 1994, Freese & Mutanen 1997, Mutanen & Freese 2001). Their 1997 study was the largest and involved a sample of 46 subjects who were given FSO to provide 5.9 g/day ALA or a fish/sunflower oil combination equal to 5.2 g/day EPA/DHA over 4 weeks. Extensive analysis of the sample throughout the intervention, as well as at the 12-week follow-up, revealed no difference in collagen-induced platelet aggregation, thromboxane production or bleeding time between the two groups, suggesting equivalent anticoagulant effects for FSO and fish oil when consumed in comparable quantities. This was despite smaller increases in EPA levels in the platelets of the subjects taking FSO.

The largest and most recent trial (Finnegan et al 2003) compared the effects of small increases in ALA (4.5 or 9.5 g/day) and EPA and DHA (0.8 or 1.7 g/day EPA + DHA) intake on blood coagulation and fibrinolytic factors over 6 months. The randomised, placebo-controlled, parallel study of 150 moderately hyperlipidaemic subjects found no significant differences in coagulation or fibrinolysis for any intervention.

Currently, the evidence is equivocal, but may indicate a minor antiaggregatory role for FSO in high doses. Further research, with more heterogeneous designs, is required to form any valid conclusion.

Endothelial function

In one 12-week study of healthy subjects aged 55–75 years, low levels of ALA (equivalent to approximately 5 mL/day of FSO) were shown to decrease some markers of endothelial activation (Thies et al 2001). More specifically, ALA decreased the plasma concentrations of soluble VCAM-1 by 16% and soluble E-selectin by 23%.

High blood pressure

In spite of a large number of studies which failed to demonstrate a relationship between ALA intake and blood pressure, a recent prospective trial, administering 8 g/day of ALA from FSO to middle-aged dyslipidaemic men over 12 weeks, produced a significant reduction in median blood pressure readings of 3–6% (≈5 mmHg) when compared to a similarly high intake of LA from safflower oil (Paschos et al 2007). The clinical significance of this result is questionable.

Lipid-lowering

The largest and most recent trial involved over 150 moderately hyperlipidaemic patients in a double-blind, placebo-controlled, 5-arm parallel design conducted over 6 months. Two groups received FSO at different doses (equivalent to 4.5 g/day and

Clinical note — Are vegetarians at risk of omega-3 deficiency?

Omnivores can obtain n-3 long-chain PUFAs in two ways: from the partial conversion of dietary ALA or directly through the consumption of fish, eggs or animal products (Li et al 1999). Lacto-ovovegetarians obtain n-3 EFAs from the conversion of plant-based ALA and a limited amount of preformed EPA and DHA from milk, dairy products and eggs; however, their EFA content is highly dependent upon animal diets. In contrast, strict vegetarians and vegans are at risk of inadequate n-3 EFA, DHA and EPA intake because they are solely reliant on plant-based ALA, which has poor conversion to n-3 EFA metabolites in the body and they have no dietary intake of preformed DHA or EPA.

This has been demonstrated in studies in which lower plasma and platelet levels of n-3 EFAs have been identified in vegetarians compared with omnivores, together with lower EPA and DHA levels (Arterburn et al 2006). For vegetarians and vegans, increased consumption and conversion of ALA has been proposed as a strategy to ensure omega-3 adequacy; however, the evidence to date suggests that this is not effective (Burdge 2004, Phinney et al 1990).

Average daily intake of ALA has been estimated at 1.3–1.5 g in the general population and may be lower in vegetarians and vegans. Based on current conversion calculations, general consumption levels already fall short of EPA and DHA requirements. Studies investigating increased ALA consumption at 9.5 g/day, the equivalent of approximately 17 mL FSO, found this increased EPA and DPA, yet failed to improve DHA concentrations, which further proves that ALA is not an effective substitute for animal-derived omega-3 EFAs (Burdge 2004).

To complicate matters, there is evidence suggesting that high intakes of ALA downregulate the delta-6-desaturase enzyme, therefore inhibiting its own conversion (Arterburn et al 2006, Gerster 1998). Vegetarian diets are also notoriously rich in the n-6 EFA, LA, which if consumed in significantly higher quantities than omega-3 will further retard conversion of ALA (Kris-Etherton & Skulas 2005). Alternatively, background omega 3 deficiency has been speculated to improve conversion efficacy, making vegetarians and vegans potentially superior converters (Arterburn et al 2006).

Vegans and vegetarians are recommended to consume additional sources of ALA, such as algae, that may contain some preformed EPA and DHA in an attempt to reduce risk of deficiency (Kris-Etherton & Skulas 2005, Li et al 1999).

9.5 g/day of ALA), two groups received bioequivalent levels of EPA/DHA and one group received LA and served as a control group. Although the higher ALA dose induced comparable changes in serum and cell membrane EPA levels to the fish oil group, ALA failed to significantly lower lipid levels, whereas EPA and DHA reduced triacylglycerides (Finnegan et al 2003).

Alternatively, a shorter study of only 2 weeks supplementing with much higher doses of FSO (60 mL/day) or sunflower oil or 130 g/day of mackerel in hypertensive males produced positive results. Subjects taking either FSO or consuming fish experienced an equal decrease in serum triglycerides, total cholesterol and LDL cholesterol (Singer et al 1986). Interestingly, FSO intake resulted in only marginal increases in EPA levels, suggesting that lipid-lowering activity is not reliant on conversion to EPA.

One possible explanation for this comes from the results of a number of trials conducted by Prasad (Prasad 1997, 1999, Prasad et al 1998), who investigated low-ALA FSO and later isolated extracts of the lignan SDG and found significant lipid-lowering effects in animal models. In rabbits, administration of the lignan at high doses produced significant changes to blood lipids, including a 33% reduction in total cholesterol, 35% reduction in LDL cholesterol and an astonishing increase of over 140% in HDL cholesterol by week 8 (Prasad 1999). As exciting as these results are, it is difficult to determine the clinical significance of these findings because the lignan content of FSO is variable. It is possible that the high dose of FSO (60 mL/day used by Singer 1986) contained a substantial amount of SDG, which could explain the effects seen; however, this is speculation.

Insulin sensitivity/metabolic syndrome

It has been proposed that FSO may be of benefit in insulin resistance (IR) based on its possible cardioprotective activities; however, direct evidence of improved insulin sensitivity remains elusive. One small study published in 1997 demonstrated improved systemic arterial compliance in 12 subjects with suspected IR, fed a high dose of ALA over 12 weeks, although an additional finding in this study was evident of slight deterioration in insulin sensitivity (Nestel et al 1997). Another study using relatively low-dose FSO (1.7 g/day ALA) in normoglycaemic adults found no changes in glycaemic response (Curran et al 2002). However, a series of more recent clinical trials examining high-dose FSO in patients with type 2 diabetes failed to demonstrate any positive effect on glycaemic control (Barre et al 2008).

Anticancer effects

Breast and colon cancer

Bougnoux et al (1994) made an important observation when they demonstrated an inverse relationship between ALA levels in breast tissue and risk of lymph node involvement and visceral metastases in breast cancer. This has been followed up with larger studies of similar design (Klein et al 2000, Maillard et al 2002) and one meta-analysis, all yielding comparable results (Saadatian-Elahi et al 2004). The data indicate that those women with the highest breast tissue concentrations of ALA have a relative

risk of breast cancer between 0.36 and 0.39, while other FA levels fail to exhibit a statistically significant relationship. Interestingly, an epidemiological study has identified an association between low consumption of ALA in humans and increased cancer deaths in general (Dolecek 1992). Currently, the only evidence from interventional studies using FSO as a chemoprotective agent is provided by animal trials, which demonstrate that dietary FSO is effective in preventing colon tumour development and malignant mammary tumours (Dwivedi et al 2005).

Prostate cancer

There is much debate surrounding research into the hypothesised link between ALA and the risk of prostate cancer. Giovannucci, a prolific prostate cancer researcher, has contributed to numerous papers on this topic, deriving data from large epidemiological or prospective cohort studies, including The Health Professionals Follow-Up, The Physician's Health Study and the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (Gann et al 1994, Giovannucci et al 1993, Leitzmann et al 2004, Mannisto et al 2003). The conclusions oscillate between a positive independent association between increased ALA intake and prostate cancer risk (Gann et al 1994, Giovannucci et al 1993, Leitzmann et al 2004) to no significant association (Mannisto et al 2003). Further support of ALA as a risk factor has come from a large Norwegian epidemiological study (Harvei et al 1997), a review by Astorg (2004) and a meta-analysis by Brouwer et al in 2004. Although the majority of published data appear to implicate ALA as a prostate cancer risk factor, it is worthy of note that none of the trials were interventional and many rely exclusively on food frequency questionnaires rather than independent biochemical indices of ALA. Other researchers have also presented sound arguments against this theory, such as those articulated by de Lorgeril and Salen (2004), which query the quality of evidence being considered, the exclusion of trials that demonstrated minor risk reduction with increased ALA intake (Schuurman et al 1999) and other weaknesses of the study designs. Additional criticisms include the lack of distinction in the sources of dietary ALA, with red meat, an independent risk factor for prostate cancer, being a major dietary source of ALA in some studies (Brouwer et al 2004). Until interventional trials are conducted, a resolution on the matter is not possible.

DOSAGE RANGE

- Anticlotting: 5.9 g/day ALA.
- Improved endothelial function: 2 g/day ALA.
- Lipid-lowering: 60 mL/day FSO.
- Reduced CHD mortality: 1–3 g/day ALA.

A key consideration with FSO supplementation is product quality. Due to the high potential for FSO to become oxidised, ingestion of inadequately manufactured or preserved FSO could result in higher intakes of peroxides. It is recommended that only refrigerated FSO packaged in opaque containers be used. Once opened, the product should be consumed within a few weeks of opening and kept stored in the fridge.

ADVERSE REACTIONS

FSO may cause loose stools and gastrointestinal distress in some individuals (Austria et al 2008). There is a report of an allergic reaction to FSO, with a 40-year-old woman experiencing ocular pruritis and weeping followed by generalised urticaria and nausea, and vomiting within 10 min of taking a spoonful of linseed oil. A subsequent skin prick test produced a positive response to linseed. It remains unclear, however, whether this patient consumed FSO or linseed oil, which is denatured and unfit for human consumption (Alonso et al 1996).

SIGNIFICANT INTERACTIONS

None known.

CONTRAINDICATIONS AND PRECAUTIONS

- Hypersensitivity to flaxseed/linseed
- Prostate cancer

There are a number of studies that link increased ALA intake with a higher risk of prostate or aggressive prostate cancer. Although the evidence is preliminary and widely debated, it is recommended that at-risk individuals avoid high-dose consumption of FSO and only consume FSO that is packaged in opaque containers and refrigerated.

PREGNANCY USE

There is no evidence to suggest safety concerns.

PRACTICE POINTS/PATIENT COUNSELLING

- Good quality, cold-pressed FSO is a good source of the essential fatty acid ALA, which is often deficient in the Western diet. Capsules are more stable than the bottled oil which must be stored in a dark bottle, refrigerated after opening and consumed within a few weeks.
- The polyunsaturated fatty acids found in FSO, particularly ALA, are precursors of eicosanoids and influence many important physiological processes. Additional actions may be attributed to the variable amount of lignan present in FSO, but which is found in higher concentrations in the actual seed.
- FSO has demonstrated anti-inflammatory, immunological, minor antiplatelet and chemopreventive effects and a range of beneficial actions within the cardiovascular system; however, large RCTs are still required to determine the role of FSO in clinical practice.
- FSO is not an adequate substitute for animal sources of n-3 EFAs. Most studies of oral FSO demonstrate only moderate increases in EPA, while DHA remains unchanged. Strict vegetarians and vegans using FSO as n-3 EFA substitute may be at risk of EPA and DHA deficiency.
- There is some evidence to suggest that daily ingestion of an additional 1–3 g of ALA (equivalent to 5 mL FSO) may reduce the incidence of some cancers and coronary heart disease mortality; however, this remains speculative.

PATIENTS' FAQs

What will this supplement do for me?

Regular consumption of flaxseed oil, in the presence of balanced linoleic acid (omega-6) intake, may reduce cardiovascular mortality and possibly reduce the risk of some cancers; however, this remains speculative.

When will it start to work?

This will depend on the dosage taken and indication for use.

Are there any safety issues?

Long-term high doses may compromise immune function in susceptible individuals.

Preliminary evidence suggests a possible link between high ALA intake and increased risk of prostate cancer; however, this is controversial.

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Folate

HISTORICAL NOTE Folic acid was isolated from spinach leaves in 1941 and synthesised in 1946; hence, its name comes from the Latin *folium*, which means leaf.

BACKGROUND AND RELEVANT PHARMACOKINETICS and CHEMICAL COMPONENTS

Folate is the generic term for a large family of chemically similar trace compounds that fall within the vitamin B group. Folate, also known as folacin and vitamin B_9, is frequently referred to as folic acid (pteroylmonoglutamic acid or PGA). This is the most oxidised and stable form and the one characteristically used in supplements and food fortification. Folate found in animal sources is present in a 'free form' and is readily absorbed; however, aside

Clinical note — A challenge to the perceived safety and superiority of synthetic folic acid?

Given its relative stability in processing and enhanced bioavailability, synthetic folic acid in food fortificants and supplements has long been regarded as more reliable than natural dietary sources for ensuring folate adequacy (Kelly 1998). This, in turn, has led to widening implementation of mandatory folate fortification programs aimed at the prevention of neural tube defects (NTDs). Recently, however, the safety of increased exposure to synthetic folic acid has been thrown into question. Individuals who consume high doses (≥ 400 μg/day) exhibit unmetabolised folic acid in their blood, a form that does not naturally occur in human physiology (Kelly 1998, Lucock 2004, Lucock 2006, Sauer et al 2009, Smith et al 2008, Sweeney et al 2007, Troen et al 2006, Wright et al 2007). While this will eventually be hepatically converted into a natural folate derivative, there is speculation regarding the interim effects, with evidence of competition between the unmetabolised folic acid and the main active folate form methyl-THF at receptors and their subsequent down-regulation on cell surfaces (Sauer et al 2009, Smith et al 2008). Particular at-risk groups identified by researchers include those individuals taking anti-folate medications, folate-replete cancer patients and elderly patients with B_{12} deficiency (Smith et al 2008, Wright et al 2007), while others question the long-term safety for the unborn fetus (Kelly 1998). Until further research is conducted in this area, the implications, however, remain unclear.

from the organ meats, animal products are notoriously poor sources. Folate found in plant foods exists in conjugated forms, which require deconjugation by zinc-dependent enzymes in the gut prior to absorption. (Kelly 1998). This step is inhibited by chronic alcohol ingestion and some foods, including oranges and legumes (Gropper et al 2009). Secondary to this difference, the average bioavailability of natural folate is half that of the synthetic form (e.g. 55–66% versus ≈ 100% (Carmel et al 2006, Kelly 1998). Small amounts of folate are endogenously produced by bacteria in the intestines, but this appears to be predominantly lost via the faeces (Gropper et al 2009).

Dietary folate and synthetic folic acid, alike, then undergo complex conversion into folate's active forms, e.g. tetrahydrofolate (THF). This occurs via a multistep pathway now proposed to occur solely within the liver (Wright et al 2007). In contrast, a less common supplemental form of folate — folinic acid (5-formyltetrahydrofolate or 5-formylTHF), as an intermediate folate metabolite, bypasses some of these steps to readily form 5,10-methylenetetrohydrofolate (5,10-formylTHF) (Kelly 1998, McGuire et al 1987, Priest et al 1991).

Secretion into the bile of the THF derivatives and their subsequent reabsorption through the enterohepatic circulation enable redistribution throughout the body. Distribution of folate appears to be regulated via an unknown mechanism, ensuring increased availability to those tissues demonstrating rapid cell division (Gropper et al 2009). Although many of the biochemical pathways in which folate is involved act to regenerate the nutrient, there is still a significant amount that is broken down and eliminated, chiefly in the urine.

FOOD SOURCES

Good dietary sources are fresh green leafy vegetables, such as cabbage and spinach, asparagus, broccoli, sprouts, mushrooms, legumes, nuts and fortified cereals and organ meats.

Food preparation and processing can destroy up to 100% of the naturally occurring folate, as it is sensitive to light and air but especially heat; therefore, raw foods, as well as fortified foods,

Clinical note — Food fortification with folate: still not enough for pregnant women?

In 1997, voluntary folic acid fortification of foods was introduced in Australia and New Zealand to improve the folate status, particularly of pregnant women. Following this, a study evaluating mean serum folate levels in over 20,000 Australian women aged 14–45 years found that although concentrations had increased by 19%, the prevalence of poor folate status in this age group had only reduced from 8.5% to 4.1% (Metz et al 2002). Several state-based studies since 1997 have shown a variety of improvements in a range of measures, including folate awareness and supplementation rates amongst Australian women (Chan et al 2008, du Plessis et al 2008, Hickling et al 2005) and corresponding reductions in NTD births have varied from 17% to 40%; however, some researchers suggest that this decrease occurred in the first 2 years following fortification and the launch of awareness campaigns, and that there has been no further reduction since this time (du Plessis et al 2008).

Although fortification programs, including the recently introduced mandatory fortification of bread flour in Australia and New Zealand (FSANZ 2007), provide some measure of protection for women of reproductive age, supplementation is still required. Unfortunately, widespread public health campaigns have had limited success and many women remain unaware of the need to take supplements prior to pregnancy, or are aware but still fail to use supplements (du Plessis et al 2008, Metz et al 2002). In Australia, only 36% and 46% of new mothers in Victoria and New South Wales, respectively, took folate supplements in 2006, with even lower rates reported for women of low socio-economic or non-English speaking backgrounds (Watson et al 2006) and women aged 20–24 years. The last group also experiences the highest rate of NTD births (du Plessis et al 2008).

are considered superior sources, which in Australia provide 100 μg per serve (Gropper et al 2009, Hickling et al 2005).

DEFICIENCY

Folate deficiency is not uncommon and can develop within only 4 months of an inadequate diet (Carmel et al 2006, Gropper et al 2009, Wilson et al 1991).

In light of folate's fundamental role in DNA synthesis, deficiency of this nutrient will predictably impact most on those cells and tissues that exhibit a high turnover (e.g. blood and the cells in the gastrointestinal tract), which also applies to those stages of development with increased rates of growth, such as pregnancy and fetal tissue development.

Signs and symptoms of deficiency

- Macrocytic/megaloblastic anaemia
- Fatigue
- Psychological symptoms such as irritability and depression (Reynolds 2002)
- Headache
- Hair loss
- Nausea
- Insomnia (Pelton et al 2000)
- Peripheral neuropathy
- Tendon hyperreflexivity
- Diarrhoea
- Weight loss
- Cerebral disturbances (Botez 1976), cerebral cortex atrophy and cognitive decline
- Increased blood levels of homocysteine

Primary deficiency

This develops in response to inadequate dietary intake and can be caused by a diet generally lacking in fresh, lightly cooked vegetables. Risk is increased in patients with *MTHFR* gene polymorphisms, in people receiving total parenteral nutrition (TPN), chronic alcoholics, phenylketonuria patients on restricted diets, patients with sickle cell anaemia and the institutionalised elderly (Carmel et al 2006, Wahlqvist 2002).

Folate enzyme polymorphisms

Single allele substitution in the gene encoding for the *N*5,10-methylenetetrahydrofolate reductase enzyme, responsible for converting folate into its methylated 'active' form, results in several possible polymorphisms. Individuals who are homozygous for the *MTHFR* C677T polymorphism (2–16% white populations) convert the active folate form at only 30% of the normal capacity, while the *MTHFR* A1298C genotype produces an enzyme with 60% of the unaffected enzyme activity (Gilbody et al 2007). Homozygotes for either polymorphism are at a significantly increased risk of folate deficiency and cannot maintain adequacy with recommended dietary intake levels (NHMRC 2006).

Secondary deficiency

Secondary deficiency is caused by compromised absorption, increased excretion or increased demands or losses. Inadequate absorption can occur in malabsorption syndromes such as coeliac and Crohn's disease, with long-term use of certain medications such as phenytoin, sulfasalazine, cimetidine, antacids and oral contraceptive pill (OCP), in congenital malabsorption states and in blind loop syndrome (Beers & Berkow 2003), especially when combined with suboptimal dietary intake (Carmel et al 2006). Significantly impaired absorption has also been observed in HIV patients (Revell et al 1991).

Besides impaired absorption, inadequate use can occur with concurrent vitamin B12 or C deficiency, smoking (Gabriel et al 2006) or acute or chronic alcoholism (Hamid & Kaur 2007). A genetic variation in folate requirement has also been identified, as a congenital enzyme deficiency exists in approximately 13% of the Western population (Ma et al 1996). In these cases, total or partial absence of the enzyme responsible for the final step in converting folate to its major active metabolite (methylenetetrahydrofolate reductase) results in decreased plasma levels (Kumar & Clarke 2002). Therefore, these individuals have a higher folate requirement than others without this congenital enzyme deficiency and display increased susceptibility to folate deficiency.

A number of pharmaceutical drugs, such as folic acid antagonists (e.g. methotrexate), can affect status by interfering with absorption, use and conversion to its active forms. In such cases, oral folic acid supplements are sometimes given to reduce side effects, although it may marginally reduce drug efficacy (Kumar & Clarke 2002, Strober & Menon 2005).

Additionally, there are several subpopulations with increased demands for folic acid, such as pregnant and lactating women, the elderly and patients with malignancies, haemolytic anaemias such as sickle cell disease, chronic exfoliative skin disorders, or achlorhydria (Gropper et al 2009). Extra losses have also been reported in haemodialysis patients.

MAIN ACTIONS

Folate's actions are all secondary to its ability to donate methyl groups and its central role, therefore, in one-carbon metabolism.

Coenzyme

As a key methyl donor, folate is involved in a variety of reactions important for the metabolism of amino acids and nucleic acids.

DNA and RNA synthesis

Folate plays an essential part in the production of purines and pyrimidines that make up DNA, making it a critical nutrient in relation to cell division and repair of genetic material, and is generally required for genomic stability. Subsequently, folate plays an indirect role in the synthesis of transfer RNA.

Production of the active form of B_{12}

Folate and B_{12} are intrinsically linked; for example, the conversion of B_{12} into methylcobalamin is dependent upon the presence of a THF derivative.

Reduction of homocysteine levels

Folate, via B_{12} activation, donates a methyl group to homocysteine facilitating its recycling back to methionine. Together with vitamin B_6, necessary for homocysteine catabolism, folate effectively lowers homocysteine levels.

Synthesis of S-adenosyl-l-methionine (SAMe)

Following regeneration of methionine from homocysteine, the methyl group donated by folate is then taken up by SAMe, enabling it to become a carbon donor in multiple transmethylation reactions throughout the body, including neurotransmitter synthesis (Hendler & Rorvik 2001).

Amino acid metabolism

Folate is involved in the synthesis of some of the non-essential amino acids such as serine and glycine. It is also required for the conversion of histidine into glutamate (Gropper et al 2009).

CLINICAL USE

The conditions for which folate is indicated as a potential treatment are primarily due to an existing deficiency, through either primary or secondary pathways. Research has focused particularly on those conditions in which folate deficiency is a consequence of medication use and the benefits of improved folate status.

Prevention and treatment of deficiency

Commonly, folic acid supplements are used to correct identifiable deficiency states, such as macrocytic anaemia, or given as preventative treatment to those patients at risk of deficiency, such as in malabsorption syndromes or taking long-term folate antagonist medication. Increased oral intake of folate has been found to be effective even in cases of malabsorption due to the passive diffusion evident with pharmacological doses (Carmel et al 2006).

Preconception and during pregnancy

Poor folate status either 1 month before conception or during the first pregnancy trimester is an independent risk factor for NTD in the newborn. One study has suggested that the increased risk could be as high as 10-fold (Daly et al 1995).

Intervention trials for pregnancy have routinely used 400 μg folic acid/day; however, there is some suggestion that routine ingestion of only 100 μg folate from fortified food would prevent the majority of NTDs. Studies have also been conducted on women with a previous NTD birth, with benefits demonstrated at doses of 4 mg/day. There is a general consensus among researchers and health authorities that due to the inconsistent nature of natural food sources, taking a supplement or incorporating fortified foods is the most reliable way to increase levels sufficiently (Cuskelly et al 1996). A maternal red blood cell folate concentration > 906 nmol/L is thought to be optimal for lowering risk (Pietrzik et al 2007).

Our understanding of the consequences of folate inadequacy during pregnancy has progressed significantly recently, with the ongoing attribution of other birth defects including Down syndrome (Eskes 2006) and cleft lip and/or palate (CL/P) (Blieka et al 2006, Badovinac et al 2007, Boyles et al 2008, Chevrier et al 2007, Johnson & Little 2008). While increased dietary folate does not appear to convey protection against CL/P (Johnson & Little 2008), one meta-analysis of five prospective studies revealed that folic acid supplementation resulted in risk reduction of 0.55 for all types of cleft presentations (Badovinac et al 2007). Interestingly, several studies have failed to demonstrate a significant relationship between the *MTHFR* C677T genotype and CL/P (Boyles et al 2008, Chevrier et al 2007); however, this may be confounded by concurrent folic acid supplementation in some individuals.

Higher folate levels are linked to the prevention of miscarriages, decreased risk of intrauterine growth retardation, increased birth weight in the offspring of smoking mothers (Sram et al 2005) and increased rates of twin pregnancies, from both natural and in vitro fertilisation (IVF) conception (Haggarty et al 2006).

OCP-induced folate deficiency

Long-term use of the oral contraceptive pill (OCP) (>5 years) has historically been associated with a progressive decrease in serum folate levels, of up to 40%, which could feasibly result in changes to cognition and mood, increased risk of macrocytic anaemia and increased risk of NTD in newborns once use has ceased. Results from recent studies suggest this last concern may be unfounded (Lussanaa et al 2003, Sütterlin et al 2003).

There are a number of proposed mechanisms for folate depletion with OCP use, including concurrent depletion of B_{12}, which is involved in the regeneration pathway of THF (Bielenberg 1991), and impaired folate resorption (Sütterlin et al 2003).

Hyperhomocysteinaemia

Together with vitamins B_{12} and B_6, folic acid has been shown to reduce high plasma levels of homocysteine (Hcy). Of the three, folate appears to have the strongest effect (Voutilainen et al 2001). Although elevated Hcy has been implicated as a risk for cardiovascular disease (including atherosclerosis and coronary artery disease), cerebrovascular disease, peripheral vascular disease and venous thromboembolism (Clarke et al 1991, den Heijer et al 1996, Malinow et al 1989, Selhub et al 1995), exudative age-related macular degeneration (Nowak et al 2005), noise-related hearing loss (Gok et al 2004), cognitive dysfunction, posttraumatic stress disorder (Jendricko et al 2008), breast cancer incidence in post-menopausal women (Gatt et al 2007) and adverse pregnancy outcomes (Bjorke Monsen & Ueland 2003) including postnatal depression (Behzadi et al 2008), clinical trials are ongoing to determine the clinical relevance of these associations.

Bone health and fracture risk

Elevated Hcy has been identified as a strong risk factor for osteoporotic fractures (Abrahamsen et al 2006, Green et al 2007, McLean et al 2008, Rejnmark

et al 2008). While a significant association between the *MTHFR* C677T polymorphism and fractures has also been demonstrated, this is only significant when coupled with low reported intake of folate, B_{12}, B_2 and B_6 (Abrahamsen et al 2006). This has led some researchers to conclude that the response rate to folate treatment amongst an osteoporotic population is likely to be as little as 2% (Abrahamsen et al 2006). This may explain the lack of positive effect on bone turnover seen in a randomised controlled trial (RCT) of hyperhomocysteinaemic (> 15 mmol/L) older patients treated with 1 mg folate, 500 μg B_{12} and 10 mg B_6 treated for 2 years, in spite of significant Hcy lowering (Green et al 2007).

Cardiovascular protection and treatment

In spite of two early meta-analyses which concluded that risk of ischaemic heart disease could be reduced by 16% following a decrease in Hcy of 3 mmol/L (Homocysteine Study Collaboration 2002, Wald et al 2002), there are few folate interventional studies in established hyperhomocysteinaemic cardiovascular populations and recent studies have produced mixed findings. An interesting trial investigating the benefits of combined B vitamins (5 mg folic acid and high-dose B complex, both administered twice weekly) to patients with a history of cardiovascular events has revealed that those participants whose Hcy decreased within the first 3 months demonstrated significantly reduced cardiovascular risk over the next 5 years; however, no protection was conveyed for slower responders (Siragusa et al 2007). While another small study of B vitamins in hyperhomocysteinaemic elderly subjects failed to improve blood pressure (McMahon et al 2007), elevated Hcy secondary to impaired kidney function in this population group cannot be excluded as a confounding variable.

Alzheimer's dementia and impaired cognitive function in the elderly

Findings such as the prevalence of folate deficiency in the elderly, increasing Hcy levels with age, evidence of an inverse relationship between total plasma Hcy levels and cognitive function, and preliminary evidence of correlation between Hcy and plasma amyloid peptides levels in Alzheimer patients (Aisen et al 2008) have attracted attempts to link the phenomena, providing an explanation for neurodegenerative disorders.

In spite of this, and a large number of investigations of B vitamins, very few have restricted participation to only hyperhomocysteinaemic individuals, which may partly explain their negative findings. The Folic acid and carotid intima-media thickness (FACIT) trial, however, administered 800 μg/day over 3 years to participants with elevated baseline Hcy (≥ 13 mmol/L), producing a mean increase in serum folate of 576% and 26% reduction in plasma Hcy (Durga et al 2007). Treated subjects demonstrated significant improvements in three of the six cognitive testing domains (memory; information processing speed and sensorimotor speed), leading the authors to conclude that folic acid is an effective agent for improving cognitive function that tends to decline with age.

In patients with organic brain disease including Alzheimer's and vascular dementia, again only one study has restricted participation to hyperhomocysteinaemic individuals, administering 5 mg folic acid together with 1 mg B_{12} daily over 2 months (Nilsson et al 2001). As this stands alone in its positive findings, it is suggestive that Hcy is a key indicator of likelihood for response to B vitamin supplementation (Nilsson et al 2001)

It is important to note that hyperhomocysteinaemic patients suffering dementia do not typically co-present with macrocytic anaemia, as might be expected (McCaddon et al 2004). Therefore, the neurological and haematological features of B_{12} and folate deficiency are often unrelated in these patients.

Renal transplant recipients

Combination vitamin B treatment (folate, B_{12} and B_6) may be of benefit in renal transplant patients, according to an RCT of 56 renal transplant patients, which found that vitamin supplementation with folic acid (5 mg/day), vitamin B_6 (50 mg/day) and vitamin B_{12} (400 μg/day) for 6 months reduced the progression of atherosclerosis, as evidenced by a significant decrease in carotid intima-media thickness. Additionally, a significant decrease in homocysteine levels was observed (Marcucci et al 2003).

Restenosis after percutaneous coronary intervention

An RCT found that treatment with vitamin B_{12} (cyanocobalamin 400 μg/day), folic acid (1 mg/day) and vitamin B_6 (pyridoxine hydrochloride 10 mg/day) for 6 months significantly decreased the incidence of major adverse events, including restenosis, after percutaneous coronary intervention (Schnyder et al 2002). In contrast, a more recent trial demonstrated an increased risk of in-stent restenosis in those patients intravenously administered 1 mg of folic acid, 5 mg of vitamin B_6 and 1 mg of vitamin B_{12} followed by daily oral doses of 1.2 mg of folic acid, 48 mg of vitamin B_6 and 60 μg of vitamin B_{12} for 6 months (Lange et al 2004). Further research with more consistent study designs is required to elucidate the true effects.

Idiopathic recurrent miscarriage (IRM)

Maternal hyperhomocysteinaemia and poor folate status are risk factors for recurrent embryo loss and for first early embryo loss (George et al 2002). There has also been conflicting evidence in relation to the role of *MTHFR* polymorphisms and pregnancy, although many studies point towards increased risk of recurrent spontaneous abortion. One explanation for the discrepant results may be that the numbers of study participants have been relatively small (Zetterberg 2004). Although researchers encourage the periconceptional use of both folate and B12 to reduce these risks, there is a lack of interventional studies in this area other than one investigation of combined aspirin (100 mg/day) and folic acid

Clinical note—Homocysteine lowering an ineffective treatment?

In spite of confirmation that elevated Hcy is an independent risk factor for cardiovascular disease, dementia and a range of other chronic conditions and the consistent finding that folic acid and B_{12}, in particular, can reduce these levels, a large number of studies examining the effect of supplementation have failed to produce clinical benefits. While this has led some researchers and clinicians to abandon Hcy-lowering strategies, including folic acid supplementation, others have reflected on possible reasons for this discrepancy. Study design critique in these trials, including the largest cardiovascular trials e.g. NORVIT and HOPE2, has identified several confounding variables and weaknesses including the following (Antoniades et al 2007, Marcus et al 2007, Maron & Loscalzo 2008):

- Samples were generally composed of individuals with only mildly elevated Hcy.
- In cardiovascular studies, patients typically had advanced pathology, e.g. recent myocardial infarction (MI) in the NORVIT study.
- Concomitant initiation of polypharmacy with B vitamins.
- The cardiovascular benefits may have been too small for the studies to detect due to incorrect powering.
- Study participants have been included even when taking B vitamins prior to commencement of and during study.
- Some study participants consumed folate-fortified diets.

Accordingly, these researchers conclude that more positive outcomes are likely if future study designs control for these confounding variables and select more suitable subjects, e.g. marked hyperhomocysteinaemia patients who are prediagnostic or in the early stages of their condition. Until the results of such trials emerge, they recommend the ongoing treatment of elevated Hcy with folate and B vitamins.

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(5 mg/alternate days) throughout gestation, on top of initial (12 weeks) prednisone and progesterone treatment (Tempfer et al 2006). This treatment yielded higher live birth rate compared with no treatment in women with IRM.

Cardiovascular disease protection and treatment independent of homocysteine status

In the absence of a causal relationship between Hcy and cardiovascular disease, what remains most promising for folate are studies illustrating its protective effects, mediated through other mechanisms. This has led some researchers to suggest that folate deficiency may be the primary cause of an increased vascular risk and that elevated Hcy levels should principally be considered an indicator of low folate status rather than a pathogenetic marker (Verhaar et al 2002). Demonstrations of in vitro antioxidant activity, effects on co-factor availability and direct and indirect interactions with the endothelial NO synthase enzyme have been proposed as plausible mechanisms, through which folate may prevent endothelial dysfunction (Antoniades et al 2007, Das 2003, Verhaar et al 2002).

Several studies show the cardiovascular protective effects of folic acid, including the predictive value of low folate status on stroke risk (Bazzano et al 2002, Verhaar et al 2002); however, on the whole, interventional studies using folate (800 μg to 2.5 mg daily) either alone or in combination with the other B vitamins have been disappointing. Two meta-analyses from 2006 assessing the impact of folate alone or in combination on cardiovascular and all-cause mortality in individuals with pre-existing cardiovascular or kidney disease concluded that the treatments conveyed no significant benefits (Bazzano et al 2002, Bleys et al 2006). More recent studies have produced equivocal results. Combined B vitamins failed to reduce cardiovascular risk in high-risk women (Albert et al 2008), improve mortality and cardiovascular event frequency in patients with coronary artery disease (Ebbing et al 2008), failed to protect against cardiovascular events over 40 months (Bønaa et al 2006) and failed to prevent vascular events in patients with a stroke history after 3.9 years (Potter et al 2008).

On a more promising note, 51 heart transplant recipients who took 15 mg/day of methyltetrahydrofolate for 1 year following transplantation were found at their 7-year follow-up to have reduced all-cause mortality with a relative risk (RR) 0.53 when compared to the placebo group (Potena et al 2008). Another small study, employing high-dose folate (10 mg/day) in patients with a recent history of acute myocardial infarction, demonstrated improved endothelial function (Moens et al 2007). These positive findings were independent of Hcy levels at baseline or changes to Hcy throughout the trial.

Cognitive decline, dementia and Alzheimer's disease prevention or treatment independent of homocysteine status

Independent of Hcy, folate is implicated in cognition and neurodegeneration due to its ability to improve nitric oxide levels in the brain and facilitate synthesis of neurotransmitters (Malouf & Grimley Evans 2008). Additionally, atrophy of the cerebral cortex results from folate deficiency. Currently, an abundance of epidemiological evidence and a limited number of studies have shown a positive correlation between folate status and dementia. For example, a 2002 review has estimated that 71% of acute hospital admissions with severe folate deficiency have organic brain syndrome, compared with 31% of controls (Reynolds 2002). Low baseline serum folate also predicted dementia in a sample of 625 individuals followed over 2.4 years (Kim et al 2008), with onset of dementia significantly associated with exaggerated declines in folate, B_{12} and increases in Hcy, which may, however, have been the result of concomitant weight loss. In spite of

this knowledge, the results of studies investigating supplemental folic acid have been equivocal and warrant closer examination of the disparate methodologies.

A review by Balk in 2007, which sub-analysed folic-acid-only treatments (three RCTs, using 750 μg to 15 mg/day over 5–10 weeks) in elderly patients who were either healthy or cognitively impaired, found that, while folic acid was not universally effective, there was evidence to suggest that patients with low baseline folate (< 3 ng/mL) may significantly benefit. In contrast, a 2008 Cochrane review examining the effects of folic acid supplementation, with or without vitamin B_{12}, including some of the same trials, concluded that folate was an ineffective treatment (Malouf & Grimley Evans 2008).

Several studies investigating folic acid, either alone or in combination with other B vitamins, for slowing cognitive decline in Alzheimer's disease have failed to demonstrate an effect, independent of the hyperhomocysteinaemic population (Aisen et al 2008). One small study using 1 mg folic acid/day in conjunction with cholinesterase inhibitors over 6 months did, however, point towards an additive effect on patients' function (rather than cognition per se) regardless of Hcy (Connelly et al 2008); however, a similar study using higher doses of combined B vitamins failed to produce any statistically significant benefits (Sun et al 2007).

Anticonvulsant-induced folate deficiency

Anticonvulsant medications such as phenytoin, carbamazepine and valproate reduce serum ftolate status. Individual studies have estimated an incidence of 15% folate deficiency in this group, compared with 2% for control groups (Froscher et al 1995). However, the figure may be as high as 97% with long-term phenytoin therapy (Rivey et al 1984). This may be due to increased use of folate in drug metabolism and/or decreased mucosal absorption (Berg et al 1992, Pelton et al 2000). Often, folic acid supplements are recommended to avoid deficiency, but this requires close supervision to ensure drug efficacy is not substantially reduced (Rivey et al 1984), and a recent series of published case reports documenting NTD births to women supplemented with folic acid 5 mg/day while on anticonvulsants has thrown into question whether this commonly recommended dose is sufficient or whether concomitant administration of other B vitamins, especially B_6, may be necessary (Candito et al 2007).

Psychiatric illness

Over the past three decades, a vast number of case reports, open studies and, to a lesser extent, case–control studies have been published on the topic of psychopathology and folate deficiency. Many report a high incidence of serum folate deficiency in patients with symptoms of depression and various psychiatric disorders, particularly in geriatric populations (Reynolds 2002). For instance, one review identified that rates of deficiency varied between 8% and 50% in patients with various psychiatric disorders including depression and schizophrenia (Young & Ghadirian 1989). Two large studies involving over 350 patients diagnosed with acute psychiatric presentations identified low folate levels or frank deficiency (31% and 12% respectively). The patients with the most marked deficiency were also the group with the highest percentage of inpatients (Carney et al 1990). Recently, another study of similar design found that 30% of 224 newly admitted psychiatric patients had low serum folate (< 3.5 ng/mL) compared to only 2.4% of controls, and that patients with low folate were 3.5-fold more likely to present with depressive features (Lerner et al 2006). Disturbingly, the researchers also identified a significant trend between folate deficiency and hospital readmissions.

Depression

Aetiological role

It has been estimated that 15–38% of depressed people are folate deficient (Alpert & Fava 1997, Lerner et al 2006). Studies have also demonstrated that low dietary folate consumption (< 256 μg/day) (Tolmunen et al 2004), low serum folate (< 3.5 ng/mL) (typically co-occurring with B_{12} deficiency) (Gilbody et al 2007, Lerner et al 2006) and an *MTHFR* C677T genotype (OR 1.36) are all independently associated with an increased risk of depression (Gilbody et al 2007, Kelly et al 2004). The lesser-studied *MTHFR* A1298C genotype (although more active than the C677T genotype, but still 40% underactive) also demonstrates a weak positive relationship with depression incidence; however, more studies are required (Gilbody et al 2007). Following on from these findings, serum folate has also been negatively correlated with depression severity and duration, in some, but not all, studies (Kim et al 2008). One proposed explanation for these inconsistencies is that low folate and elevated Hcy are only found in a sub-group of depressed patients; in particular, those who experience increased anger and hostility as part of their depression (Fraguas et al 2006).

Additional studies also highlight an association between antenatal and postnatal depression and elevated Hcy or low folate levels but not serum B_{12} nor dietary intake of these two nutrients (Abou-Saleh et al 1999, Miyake et al 2006) and depression in antenatal and postnatal patients, with Hcy naturally peaking in the 3rd trimester (Abou-Saleh et al 1999, Behzadi et al 2008). The link between folate and B_{12} and depression has been hypothesised to be via Hcy and independent of this, due to its methylation role generally (Bottiglieri 2005, Coppen & Bolander-Gouaille 2005, Das 2008, Lerner et al 2006, Gilbody et al 2007, Roberts et al 2007, Tiemeier et al 2002).

Therapeutic role

Given the volume of evidence linking folate with depression, it is surprising that so few clinical trials have been conducted. A Cochrane systematic review of three RCTs involving 247 depressed people suggested that, on the limited evidence available, folate shows potential as an augmenting

agent, but speculated that its effectiveness might be restricted to folate-deficient patients (Taylor et al 2003). The studies included in this review used 500 μg folic acid, 15 mg or 50 mg of methyltetrahydrofolate once daily and lasted from 8 weeks to 6 months.

More recent studies, particularly in the elderly, who exhibit high rates of both folate deficiency and depression, have investigated the effects of broad-scale nutritional supplementation (meeting recommended daily intakes (RDIs) for all essential micronutrients) over a 6-month period with promising results. Red cell folate and serum B_{12} values rose in supplemented individuals in accord with significantly reduced scores on depression scales (Gariballa & Forster 2007). Prophylactic treatment of non-depressed elderly men with 2 mg folic acid, 25 mg B_6 and 400 μg B_{12}, in another study, however, failed to reduce depression incidence over 2 years (Ford et al 2008).

Improves response to standard antidepressants

Research investigating folate's adjunctive role in depression treatment has escalated in recent years and there is now evidence of an impaired fluoxetine response in patients with low folate levels, with response rates dropping from 44.7% in subjects with normal serum folate to only 7.1% of deficient patients (< 2.5 ng/mL) (Papakostas et al 2004a, 2004b), as well as a potentiating effect when only 500 μg/day of folic acid is added to fluoxetine (Coppen & Bailey 2000). Reduced folate levels have also been associated with reduced response to sertraline (Alpert et al 2003). Poor folate status negatively impacts response time (+1.5 weeks) (Papakostas et al 2005) and relapse rates during continuation of fluoxetine (42.9% relapse in patients with low folate levels versus 3.2%) (Papakostas et al 2004a, 2004b), independent of B_{12} and Hcy levels.

Schizophrenia

Folate has been implicated in schizophrenic aetiology since the 1950s with one-carbon metabolism abnormalities proposed as a distinct hypothesis at a similar time (Regland 2005). With current knowledge linking the two, there has been renewed interest in the role of folate in this disorder. In particular, folate deficiency fits with the neurodevelopmental theory, implicating malnutrition amongst other environmental stressors during gestation in the subsequent susceptibility to neurological disorders of offspring (Applebaum et al 2004, Gilbody et al 2007, Haidemenos et al 2007, Muntjewerff & Blom 2005). Specifically, elevated Hcy in the third trimester has been associated with significantly elevated risk. This theory is supported in part by the parallel increases in NTD births and schizophrenia incidence in populations affected by famine (Muntjewerff & Blom 2005). Further evidence of folate's role comes from elevated Hcy and a high incidence of the *MTHFR* C677T genotype which are frequently, but not consistently, found in this patient group (Kemperman et al 2006, Regland 2005). A recent meta-analysis of links between this folate polymorphism and schizophrenia found an odds ratio of 1.44 (Gilbody et al 2007).

Several studies in adult schizophrenic patients have reported increased rates of active folate deficiency. One, in addition to this, demonstrated an inverse relationship between serum folate and degree of negative symptoms and a positive association between Hcy and extra-pyramidal symptoms (Goff et al 2004). There have been several case reports of successful treatment using 15–30 mg folate together with B_{12} injections (1 mg every 10 days) and *N*-acetylcysteine (200 mg twice daily) (Regland 2005) and a more recent study which administered a combination of 2 mg folic acid, 25 mg B_6 and 400 μg B_{12} to schizophrenic patients with baseline Hcy > 15 mmol, which produced improvements in both clinical features and neuropsychological test performance (Levine et al 2006).

Other psychiatric presentations

Significantly decreased red cell folate (not serum) has been documented in both phases of bipolar disorder (Hasanah et al 1997), as well as frequently found in patients chronically treated with lithium (Coppen & Bolander-Gouaille 2005). There is also preliminary evidence of mildly elevated Hcy in post traumatic stress disorder (PTSD) sufferers; however, more thorough investigation is required to confirm this tentative association (Jendricko et al 2008).

Chemopreventative role

Epidemiological, animal and human studies all suggest that folate status affects the risk of developing cancers in selected tissues; however, the exact nature of this relationship continues to elude researchers (Bollheimer et al 2005, Powers 2005). One current theory points to the negative synergism between ageing and folate inadequacy, producing aberrations in one-carbon transfer such as gene hypomethylation, implicated in potentially carcinogenic genomic changes (Jang et al 2005).

Previously, high folate intake was purported to have an almost universally protective effect. An extensive review of the role of the *MTHFR* C677T polymorphism in cancer risk concluded that, in spite of the poor folate status associated with this polymorphism, however, many studies identify it as protective against a range of cancers (Sharp & Little 2004). In addition to this, a group of Swedish researchers have demonstrated that the relationship between serum folate and colorectal cancer follows a bell-shaped curve distribution (Van Guelpen et al 2006). Speculation regarding the role of additional co-factors involved in folate activity has also emerged (Powers 2005).

Folate's actions, however, still constitute a plausible cancer risk modulator, due to its critical role in the production, methylation and repair of DNA, regulation of cell turnover and suppression of excessive proliferation (Choi & Mason 2000, 2002).

Colon cancer

The link between folate status and colorectal cancer was first suggested as a result of 1990s epidemiological findings. Subsequent rodent studies further

strengthened the theory, when chemically induced colorectal carcinogenesis was shown to be enhanced under dietary folate deprivation and reduced with folate administration (Cravo et al 1992, Kim et al 1996). Recently the *MTHFR* C677T genotype has been identified as a risk factor (OR 1.34), compounded by dietary folate below median intakes (Murphy et al 2008).

In 2005, a major review of in vitro, animal and various clinical and epidemiological studies concluded that high folate intake does not possess an independent, overall chemopreventative effect on colorectal carcinogenesis, irrespective of two large studies that suggest that folate deficiency might have a particular impact on proximal colon cancer in females (Bollheimer et al 2005). In fact, over the previous few years, the evidence pertaining to a relationship between folate and colorectal cancer derived from studies using folic acid supplementation (≈ 1 mg/day) has swung more towards one of increased risks (Cole et al 2007, Luebeck et al 2008). Consistent with this, researchers have speculated that a rise in colorectal cancer diagnoses in the US between 1996 and 1998 may be the result of mandatory fortification, which occurred during the same period (Mason et al 2007). A study based on a mathematical model, designed to investigate the effect of folic acid supplementation on colorectal cancer incidence in the general population, has concluded that folic acid would convey protective benefits only when initiated prior to 20 years of age and when initiated after this time, may in fact increase risk (Luebeck et al 2008). In spite of this, a recent study of two large prospective cohorts failed to demonstrate a relationship between prediagnostic (3–5 years) higher plasma folate and increased risk (Wolpin et al 2008).

Recent research is also taking into account a possible role for other B vitamins in the folate and colorectal cancer equation, with preliminary evidence of superior protective effects when folate is used in combination with B2 as a minimum (5–10 mg/day) (Mason et al 2008, Powers 2005).

Breast cancer

While the epidemiological evidence with respect to dietary folate and breast cancer risk has produced equivocal results, more consistent evidence points to low folate intake as a risk factor only when combined with increased alcohol consumption (Larsson et al 2007, Mahoney et al 2007). This negative synergy is further supported by evidence that maintaining adequate folate intake, usually via supplementation, can reduce or eliminate the excess risk due to increased alcohol consumption (Mahoney et al 2007). A comparable detrimental additive effect has been demonstrated between the *MTHFR* genotype and low folate intake (OR 2.80) (Suzuki et al 2008).

Cervical cancer

Folate deficiency may increase the risk of cervical cancer in individuals infected with high risk human papiloma virus (HR-HPV) (Piyathilake et al 2004). Recent evidence suggests a diet rich in fruit and vegetables generally (OR 0.52), and folate independently (OR 0.55) reduces the risk of developing cervical cancer (Ghosh et al 2008); however, much of the other evidence pertaining to a protective relationship has been ambiguous and results from intervention studies on cervical cancer have been inconsistent (Henao et al 2005, Kwanbunjan et al 2005, Sedjo et al 2003). The most surprising finding recently is that the *MTHFR* genotype appears protective against cervical cancer (Shekari et al 2008), enhanced further by a concomitant low intake of B2 (Piyathilake et al 2007).

The most promising RCT involved 47 patients taking an OCP who demonstrated mild to moderate intraepithelial dysplasia. A dose of 10 mg folic acid daily over 3 months resulted in significantly lower biopsy scores in the treatment group and a significant reduction in cytology scores from baseline (Butterworth et al 1982). Other studies have shown that folic acid treatment does not alter the course of disease in patients with pre-established cervical dysplasia (Childers et al 1995).

Other cancers

A protective role for folate in the prevention of a growing number of other cancers, e.g. prostate (Marchal et al 2008), lung (Suzuki et al 2007), pancreas (Suzuki et al 2008) and nervous system cancers (Sirachainan et al 2008), has been tentatively made, often in combination with increased alcohol consumption; however, more research is required to validate these preliminary findings.

Periodontal disease

A series of RCTs have shown that rinsing with a solution of folate (5 mg/dose) twice daily alleviates gingival inflammation in all age groups and in pregnant and non-pregnant women (Pack 1984, Thomson & Pack 1982). Treatment results in a significant reduction in inflammation without altering plaque levels or folate serum status and appears to be more successful than oral supplements (Vogel et al 1976).

Preliminary evidence suggests that topical folate may also have a role in controlling gingival hyperplasia associated with long-term phenytoin use (Drew et al 1987).

Methotrexate toxicity

Methotrexate is a cytotoxic drug with folate antagonist properties. In part, its efficacy is dependent on this effect, but severe deficiency symptoms such as macrocytic anaemia are sometimes induced (Lambie & Johnson 1985). Co-administration of folic acid or folinic acid has been investigated as preventative treatment, with both forms capable of reducing drug side effects (Ortiz et al 1998, Strober & Menon 2005).

Sickle cell anaemia

In the past, folate supplements were recommended to patients with sickle cell anaemia, but more recent studies show that clinically significant folate deficiency occurs in a very small percentage of these

patients and other nutrients may be indicated (Reed et al 1987).

Vitiligo

Although a number of uncontrolled studies testing combination treatments have been promising, folate has never been assessed as a sole treatment. As such, it is difficult to determine its role in the treatment of this condition. In previous studies, a combination of oral folic acid and vitamin B_{12}, together with increased sun exposure, has produced response rates in the vicinity of 50% (Juhlin & Olsson 1997). A more recent controlled study by a different group of researchers found that exposure to a specific band width of UV radiation produced repigmentation in 92% of subjects, irrespective of vitamin supplementation (Tjioe et al 2002).

DOSAGE RANGE

Australian RDI (NHMRC 2006).

- 400 μg/day for adults; up to 1 mg/day in deficiency states.
- Up to 600 μg/day is recommended as the Suggested Dietary Target to reduce chronic disease risk in adults.
- 600 μg/day in pregnancy.
- 500 μg/day during lactation.

According to clinical studies

- Preconception care or early pregnancy supplementation: 400–600 μg/day.
- Preconception and pregnancy supplementation in women with a previous NTD birth: 4 mg/day.
- Idiopathic recurring miscarriage: aspirin (100 mg/day) and folic acid (5 mg/alternate days) throughout gestation plus prednisone and progesterone treatment for first 12 weeks.
- Anticonvulsant-induced deficiency: 15 mg/day (under supervision).
- Prevention of cervical cancer: 800–10,000 μg/day.
- Prevention of breast cancer in high alcohol consumers: 400 μg/day.
- Alzheimer's dementia in the presence of elevated Hcy: 800 μg/day.
- Alzheimer's dementia with normal Hcy: 1 mg/day in combination with cholinesterase inhibitors.
- Cognitive decline in elderly with folate deficiency: 750 μg/day.
- Depression: minimum of 2 mg or sufficient dose to reduce elevated homocysteine as stand-alone treatment.
- Depression as an augmenting agent with standard antidepressants: 500 μg/day.
- Acute psychiatric presentation: 15–30 mg methylfolate daily in combination with standard psychotropic treatment.
- Hyperhomocysteinaemia: 500–5000 μg/day.
- Cardiovascular protection in patients with elevated Hcy: 5 mg/day with high-dose B complex.
- Cardiovascular protection in heart transplant recipients or patients with recent history of MI: 10–15 mg/day.
- Methotrexate toxicity: 5 mg/week.
- OCP-induced folate deficiency: 2 mg/day.
- Periodontal disease: rinse mouth with a solution of folate (5 mg/dose) twice daily.
- Prevention of restenosis after percutaneous coronary intervention: 1 mg in combination with vitamin B_{12} (400 μg) and vitamin B_6 (10 mg) daily.
- Schizophrenia with marked negative symptoms: 2 mg/day in combination with 25 mg/day B_6 and 400 μg/day B_{12}.
- Sickle cell anaemia: 1 mg/day.
- Ulcerative colitis: 15 mg/day.
- Vitiligo: 2–10 mg/day.

ADVERSE REACTIONS

Adverse reactions appear to be limited to oral doses greater than 5 mg/day. Reactions include a generalised urticaria associated with an allergic response, nausea, flatulence and bitter taste in the mouth, irritability and excitability.

SIGNIFICANT INTERACTIONS

Antacids

Reduce folic acid absorption — separate doses by 2–3 hours.

Anticonvulsants (phenytoin)

Reduced folate levels frequently develop with long-term use, but macrocytic anaemia is rare (Lambie & Johnson 1985). Supplementation can reduce toxicity, which is a beneficial interaction, although medical supervision is advised.

Cholestyramine (e.g. Questran)

Reduced folate absorption — observe patient for signs and symptoms of folate deficiency and separate doses by at least 4 hours.

Gastric acid inhibitors (proton-pump inhibitors)

Reduced folic acid absorption — separate doses by 2–3 hours.

Methotrexate

Methotrexate is a folate antagonist drug. Folate supplementation can reduce toxicity, which is a beneficial interaction; however, it may reduce the efficacy of methotrexate — medical supervision advised.

Oral contraceptives

Folate levels are reduced with long-term use of the OCP, particularly those with high oestrogen content; therefore, increased intakes may be required for women undertaking long-term use.

Pancreatin

Reduced folate absorption (Kelly 1998) — separate doses by 2–3 hours.

Pyrimethamine (e.g. maloprim)

Impairs the use of folate and, as such, supplementation with folinic acid may be beneficial.

Sulfasalazine

Folic acid can reduce drug absorption — separate doses by 2–3 hours.

Trimethoprim
Trimethoprim is a folate antagonist drug. Supplementation can reduce toxicity, which is a beneficial interaction — medical supervision advised.

Zinc
At high doses (>15 mg/day), minor zinc depletion may develop (Carmel et al 2006, Kelly 1998) — observe patients for signs and symptoms of zinc deficiency.

CONTRAINDICATIONS AND PRECAUTIONS
Use of folate supplements may mask a B_{12} deficiency state by correcting an apparent macrocytic anaemia without altering progression of neurological damage. It is recommended that patients be screened for vitamin B_{12} deficiency.

PREGNANCY USE
According to the Australian Drug Evaluation Committee (1999), folate is considered to be safe to take during both pregnancy and lactation. Retrospective analysis of a trial of folate in pregnancy in the 1960s has suggested a possible increase in all-cause mortality and breast cancer in pregnant women taking 5 mg/day folate; however, this finding could be due to a number of factors unrelated to folate (Bland 2005, Charles et al 2004). The only context requiring special consideration is those pregnant women taking anticonvulsant medication (see *Significant interactions*).

PRACTICE POINTS/PATIENT COUNSELLING
- Folate is involved in a number of important biochemical pathways required for health and wellbeing, in particular development and cell growth.
- Folate supplements are often given to correct deficiencies or prevent deficiency in people at risk, such as those with malabsorption syndromes (e.g. coeliac disease and Crohn's disease), long-term use of certain medications such as phenytoin, sulfasalazine, cimetidine, antacids and the OCP, in congenital malabsorption states and blind loop syndrome, chronic alcoholism, the institutionalised elderly, pregnant and lactating women and HIV infection.
- It is considered to be the most important supplement to be taken by women in the weeks leading up to conception and during the first 12 weeks of pregnancy, in order to significantly reduce the risk of NTD in newborns. Food fortification is not considered sufficient.
- Other uses for folic acid supplements include reducing homocysteine levels (often in combination with vitamins B_{12} and B_6), reducing primary cardiovascular disease risk and cancer risk in general, periodontal disease (as a topical application), depression, schizophrenia and other psychiatric presentations and vitiligo.

PATIENTS' FAQs
What will this supplement do for me?
Folic acid is essential for health and wellbeing. Supplements have a critical role in preventing NTD in newborns and may also reduce the risk of primary cardiovascular disease and improve brain function in Alzheimer's dementia and non-Alzheimer's dementia and depression. It can also reduce the toxic effects of some medicines and may reduce the risk of developing some forms of cancer.

When will it start to work?
This depends on the indication.

Are there any safety issues?
The major concern with high doses of folate is that they may mask an underlying vitamin B_{12} deficiency and allow it to progress unnoticed, which means that a vitamin B_{12} deficiency should be excluded. It also interacts with some drugs in both a potentially harmful and a beneficial way. High doses should not be used in patients with a history of bowel polyps or adenomas.

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Garlic

HISTORICAL NOTE Garlic has been used as both a food and a medicine since antiquity. Legend has it that garlic was used in ancient Egypt to increase workers' resistance to infection and later used externally to prevent wound infection. Other ancient civilisations have also used it medicinally. Sanskrit records document the use of garlic approximately 5000 years ago and the Chinese have been using it for over 3000 years. One of the uses of garlic was as a treatment for tumours, a use that extends back to the Egyptian Codex Ebers of 1550 BC (Hassan 2004). Louis Pasteur was one of the first scientists to confirm that garlic had antimicrobial properties. Garlic was used to prevent gangrene and treat infection in both world wars. Traditionally, garlic has been used as a warming and blood-cleansing herb to prevent and treat colds, flu, coughs and menstrual pain and expel worms and other parasites.

COMMON NAME
Garlic

OTHER NAMES
Ail, ajo, allium, camphor of the poor, da-suan, knoblauch, la-juan, poor man's treacle, rustic treacle, stinking rose

BOTANICAL NAME/FAMILY
Allium sativum (family Liliaceae)

PLANT PART USED
Bulb, and oil from the bulb

CHEMICAL COMPONENTS
Garlic bulbs contain organosulfur compounds (OSCs), protein (mainly alliinase), amino acids (such as arginine, lysine, threonine and tryptophan), fibre, lipids, phytic acid, saponins, beta-sitosterol and small quantities of vitamins and minerals such as vitamin C, vitamin E, beta-carotene, chromium, iron and selenium (Duke 2003). Of the numerous constituents present, it is the alliin component and resultant degradation products, such as allicin and ajoene, that produce much of the herb's pharmacological activity. These are formed when garlic is crushed or chewed and alliin is exposed to the enzyme alliinase. According to Commission E, 1 mg of alliin produces 0.458 mg of allicin (Blumenthal et al 2000). Allicin is unstable and degrades to various sulfides depending on the conditions. Steam distillation converts water-soluble thiosulfanates to lipid-soluble diallyl sulfides, whereas oil maceration results in the production of ajoenes and vinyldithines (Stargrove et al 2008).

The pharmacological actions of the herb are due to its organosulfur components: alliin, allyl cysteine, allyl disulfide, and allicin (Chung 2006). In garlic oil, there are three major OSCs: diallyl trisulfide (DATS), diallyl sulfide (DAS) and diallyl disulfide (DADS) (Liu et al 2006).

MAIN ACTIONS

Antioxidant
Garlic and many of its constituents have strong antioxidant activity and is capable of directly scavenging free radicals, and indirectly by enhancing endogenous antioxidant systems such as glutathione, superoxide dismutase, catalase and glutathione peroxidase (Arhan et al 2009). This has been demonstrated in vitro and in vivo (Arhan et al 2009).

When tested individually, the four main chemical classes of garlic, allyl disulfide, alliin, allicin and allyl cysteine, have been shown to exhibit different patterns of antioxidant activity. Alliin scavenges superoxide via the oxanthine oxidase system, alliin, allyl cysteine and allyl disulfide act as hydroxyl scavengers and allyl disulfide prevents lipid peroxidation (Chung 2006). S-allylcysteine has also been shown to scavenge reactive oxygen and nitrogen species, including superoxide anion, hydrogen peroxide, hydroxyl radical and peroxynitrite anion (Medina-Campos et al 2007).

According to in vitro tests, garlic prevents cadmium- and arsenic-induced oxidative damage by inducing endogenous antioxidant defence mechanisms (Chowdhury et al 2008, Ola-Mudathir et al 2008, Suru 2008).

Antioxidant activity and lower levels of oxidative stress has further been demonstrated in several clinical studies for garlic supplementation. One study used a dose of garlic 0.1 g/kg/day for 1 month, which was shown to induce a significant reduction in erythrocyte malondialdehyde (an indicator of oxidative stress) and significantly increase levels of superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) (Avci et al 2008). Similarly, oral garlic (250 mg/day) taken for 2 months caused a significant reduction in markers of lipid peroxidation in people with essential hypertension compared to normotensive controls (Dhawan & Jain 2005).

Protection against ischaemic and reperfusion injury
Prophylactic administration of garlic protects against renal and hepatic ischaemia/reperfusion injury in vitro and in a rat model (Kabasakal et al 2005, Sener et al 2005) prevents ischaemic and perfusion injuries after testicular torsion and detorsion in rats (Unsal et al 2006).

Anti-inflammatory activity
Fresh garlic extracts and garlic oil exert anti-inflammatory action in various models. Mechanisms of action identified to date include a direct action upon toll-like receptor-mediated signalling pathway inhibiting NF-kappa activation (Youn et al 2008), modification of the expression of cyclo-oxygenase (COX) activity (Thomson et al 2000), and suppression of iNOS and NO production (Liu et al 2006).

Lee et al investigated the anti-inflammatory action of DAS in articular chondrocytes and synovial fibroblasts harvested from patients undergoing joint replacement for osteoarthritis. Incubation with DAS inhibited the up-regulation of COX-2 expression in synovial cells and chondrocytes and ameliorated crystal-induced synovitis through the inhibition of NF-kappaB (Lee et al 2009).

Inhibits platelet aggregation and antithrombotic effects

In vitro studies indicate that garlic inhibits platelet aggregation through multiple mechanisms, including inhibition of COX activity, and as such, thromboxane A2 formation, via the suppression of intraplatelet Ca^{2+} mobilisation and by increasing cAMP and cGMP levels. The antioxidant action of garlic also increased platelet-derived NO, and interaction with GPIIb/IIIa receptors reduces platelets' ability to bind to fibrinogen (Allison et al 2006, Chan et al 2007, Rahman 2007).

Importantly, the method of garlic preparation can influence its antiplatelet activity in humans (Lawson et al 1992, Rahman & Billington 2000) yet microwaving, oven heating at 200°C or submersion in boiling water for 3 min has shown no reduction in inhibition of platelet aggregation as compared to raw garlic (Cavagnaro et al 2007).

A recent double-blind, placebo-controlled crossover study of 14 volunteers concluded that solvent-extracted garlic oil had minimal or no effect on platelet aggregation. Researchers found that administration of garlic 9.9 g over 4 h exerted little or no effect on both collagen and adenosine 5'-diphosphate (ADP)-induced aggregation. Adrenaline-induced aggregation did, however, exert a slight but significant ($P < 0.05$; 12) reduction (Wojcikowski et al 2007).

Stimulates fibrinolysis

A significant increase in fibrinolysis has been observed in several clinical tests for both raw and fried garlic, which appears to be dose-dependent (Bordia et al 1998, Chutani & Bordia 1981, Gadkari & Joshi 1991). A recent controlled animal study found a statistically significant decrease in plasma fibrinogen and increase in clotting time in treatment groups receiving doses of raw garlic 750 and 1000 mg/kg, respectively, in comparison to that of 500 mg/kg (Gorinstein et al 2006). Odourless garlic has been shown to stimulate fibrinolytic activity via accelerated tissue plasminogen activator (t-PA)-mediated plasminogen activation and to inhibit the formation of thrombin, leading to suppression of coagulation (Fukao et al 2007).

Anti-atherosclerotic activity

Evidence from in vitro, animal and human research has shown that garlic supplementation significantly reduces the atherosclerotic process (Campbell et al 2001, Durak et al 2002, Ferri et al 2003, Koscielny et al 1999, Kwon et al 2003, Orekhov et al 1995). More specifically, garlic significantly decreases accumulation of aortic tissue cholesterol, fatty streak formation and the size of atherosclerotic plaque in vivo (Campbell et al 2001).

The adherence of leucocytes/monocytes to endothelium is also implicated in early stage atherogenesis. In vitro studies have shown that incubation with garlic compounds significantly inhibits the oxidation of low-density lipoprotein (LDL) (Lau 2006), prevents adhesion of monocytes to IL-1alpha-stimulated endothelial cells (Rassoul et al 2006) and suppresses oxidised LDL-mediated leucocyte adhesion to human endothelial cells (Lei et al 2008). A critical review conducted on in vitro studies has confirmed that garlic inhibits enzymes involved in lipid synthesis, platelet aggregation, oxidisation of LDL while increasing antioxidant status (Rahman et al 2006).

Results from several published animal studies further confirm antiatherogenic effects and have investigated the mechanisms responsible (Durak et al 2002, Ferri et al 2003, Kwon et al 2003). One in vivo study found that garlic activated antioxidant systems and decreased peroxidation in aortic tissue (Durak et al 2002), whereas ajoene inhibited smooth muscle cell proliferation in another (Ferri et al 2003). The administration of 9 mg/kg of pure allicin in an animal model was found to reduce atherosclerotic plaque, Cu^{2+} binding to LDL, macrophages and the inhibition of LDL and oxidised LDL degradation. Allicin was also found to directly bind to lipoproteins, suggesting a further mechanism of action (Gonen et al 2005).

Similar results have been obtained using ultrasound techniques in a randomised, double-blind, placebo-controlled clinical trial, involving 152 people (Koscielny et al 1999). Not only did high-dose garlic powder significantly reduce arteriosclerotic plaque volume, it also induced a slight regression in plaque spread within the 4-year test period. Later, these results were found to be significant only in females.

In a multifactor prognostic evaluation of high-risk patients assessing risk of coronary heart disease (CHD), myocardial infarction (MI) and sudden death, prolonged administration of Allicor significantly reduced multifactor risk of CHD in both genders. However, reduced risk of MI and sudden death was achieved significantly in men but not in women (Sobenin et al 2005). A pilot study suggests that incremental benefits were identified when evaluating the role of garlic therapy in coronary artery calcification with patients also on concomitant statin therapy (Budoff 2006).

A recently published review suggested that the anti-atherosclerotic action of garlic, while dose dependent, is a valuable component in an atherosclerosis-preventing diet (Gorinstein et al 2007). A need for the standardisation of garlic products has been called for, to enable the opportunity to evaluate and draw conclusions from research findings (El-Sabban & Abouazra 2008).

A possible role for garlic in the prevention of cerebrovascular damage has been postulated through a reduction in levels of beta-amyloid (Abeta) and apoptosis, associated with the pathogenesis of Alzheimer's disease (Borek 2006). Aged S-allyl-L-cysteine, an organosulfur compound purified from aged garlic extract, exerted an anti-amyloidogenic activity in

vitro protecting against amyloid-beta-induced neuronal cell death, inhibiting amyloid-beta fibril formation and defibrillating amyloid-beta preformed fibrils (Gupta & Rao 2007, Gupta et al 2009, Imai et al 2007, Ishige et al 2007).

Reduces serum cholesterol levels

A 2000 meta-analysis of 13 clinical trials concluded that garlic is superior to placebo in reducing total cholesterol levels, exerting a modest effect (Stevinson et al 2001). In addition, a critical review published in 2006 suggests that garlic and its constituents exert a capacity to inhibit the enzymes involved in cholesterol and fatty acid synthesis, particularly mono-oxygenase and 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase (Rahman et al 2006).

A 75% inhibition of cholesterol synthesis was achieved in garlic-treated human hepatoma cells without any evidence of cytotoxicity. Results indicated that compounds containing allyl-disulfide or allyl-sulfhydryl have the strongest inhibitory effect, likely through mediation of sterol 4-alpha-methyl oxidase (Singh et al 2006). Administration of high-dose (500 mg/kg) raw garlic extract to rats showed a significant (38%) reduction in triglycerides and cholesterol (Thomson et al 2006).

The capacity for modulating lipids may be attributed to the release of allicin through enzyme activation. A clinical crossover study involving 50 renal transplant patients involved the ingestion of one garlic clove daily for 2 months, either by swallowing or chewing. The swallowing route achieved a significant reduction in systolic blood pressure (SBP) and malondialdehyde (MDA) but no change in lipid parameters. However, chewing garlic achieved a reduction in cholesterol and a significant reduction in triglycerides, MDA and systolic and diastolic blood pressures, but no changes in HDL or LDL (Jabbari et al 2005).

Garlic's beneficial effects on serum lipids have been shown to decline following cessation of treatment, suggesting that long-term supplementation is required. A reduction in cholesterol and triglycerides and increase in HDL was achieved in 30 participants with elevated blood cholesterol ingesting 5 g of raw garlic twice daily for 42 days. However, following a 42-day washout period, cholesterol and triglycerides increased and HDL decreased (Mahmoodi et al 2006). Clinical evidence also suggests that it raises HDL levels and reduces triglyceride levels (Bordia et al 1998, Sobenin et al 2005).

Hypoglycaemic activity

Animal studies have shown that garlic and its constituents exhibit a hypoglycaemic action (Jelodar et al 2005, Hattori et al 2005) and produce significant changes in glucose tolerance and insulin secretion (Liu et al 2005). An antioxidant isolated from garlic, S-allyl cysteine sulfoxide, was found to stimulate insulin secretion from beta cells in rats (Augusti & Sheela 1996). Oral administration of garlic extract for 14 days significantly decreased serum glucose in streptozotocin-induced diabetic rats but not in normal rats. The garlic extract was also compared to that of glibenclamide, a known antidiabetic drug, and was found to be more effective (Eidi et al 2006). A similar study using garlic oil found no effect on oral glucose tolerance, but did report significantly improved oral glucose tolerance at 4, 8, 12 and 16 weeks, respectively (Liu et al 2006). A recently published animal investigation suggests that garlic is insulinotropic rather that hypoglycaemic (Islam & Choi 2008).

One double-blind study reported that 800 mg garlic powder taken daily for a period of 4 weeks reduced blood glucose concentrations by 11.6% (Kiesewetter et al 1993). However, a more recent study using a higher dose of 3 g/day over 26 weeks found no effects (Ali & Thomson 1995).

The metabolic action of Allicor was investigated in a 4-week, double-blind, placebo-controlled study of 60 type 2 diabetic patients, resulting in better metabolic control due to the lowering of fasting blood glucose, serum fructosamine and serum triglyceride levels (Sobenin et al 2008). A review suggests the need for large-scale clinical studies with diabetic patients to elucidate garlic's possible role in prevention and treatment of diabetes (Liu et al 2007).

Antihypertensive activity

Numerous clinical studies have identified antihypertensive activity with garlic (Andrianova et al 2002, Dhawan & Jain 2005, Silagy & Neil 1994). Although the mechanism of action has not been fully elucidated, evidence from in vivo research suggests that both the renin–angiotensin system and the NO system are responsible for this activity (Al-Qattan et al 2006, Mohamadi et al 2000). A controlled animal study found that both raw and aged garlic produced a reduction in induced elevated SBP compared to control. A reduction in pulse pressure was also achieved in the aged garlic-treated group (Harauma & Moriguchi 2006). Rats receiving a conjugate of allicin and captopril (allylmercaptocaptopril) showed a greater reduction in blood pressure and improved cardiac hypertrophy than those receiving captopril alone. Allylmercaptocaptopril improved, whereas captopril impaired fasting glucose tolerance (Ernsberger et al 2007).

In a controlled human study, hypertensive and normotensive patients received 250 mg daily for 2 months. A moderate reduction in blood pressure and a significant reduction in NO levels were observed in the hypotensive patients compared to controls (Dhawan & Jain 2005).

Enhances microcirculation

Jung et al (1991) found that 5 h after the administration of garlic powder (Kwai: total dose 900 mg garlic powder), a significant increase in capillary skin perfusion (55%) occurred in the healthy volunteers, whereas Kiesewetter et al (1993) showed a 48% increase with a dose of 800 mg garlic.

Antimicrobial and immune-enhancing activities

Garlic and its components have been demonstrated in vitro to exert a direct and indirect activity against various pathogens, including bacteria

(both gram-negative and gram-positive), fungi and parasites. Antimicrobial sensitivity tests conducted on *Escherichia coli*, *Shigella* spp, *Salmonella* spp and *Proteus mirabilis* found that no isolates were resistant to garlic; moreover, gram-negative isolates were found to be highly sensitive to garlic in comparison to ciprofloxacin and ampicillin (Eja et al 2007).

Allicin was initially believed to be chiefly responsible for the antimicrobial activity of garlic. Research found it to exert antibacterial activity against a wide range of gram-negative and gram-positive bacteria, including multidrug-resistant enterotoxicogenic strains of *Escherichia coli*, *Staphylococcus aureus*, *Mycobacterium tuberculosis*, *Proteus* spp, *Streptococcus faecalis* and *Pseudomonas aeruginosa*; antifungal activity, particularly against *Candida albicans*; antiparasitic activity against some of the major human intestinal protozoan parasites such as *Entamoeba histolytica* and *Giardia lamblia* and antiviral activity (Ankri & Mirelman 1999, Davis 2005, Tessema et al 2006). Allicin has been found to exert an antimalarial action in vitro and in vivo (Coppi et al 2006). Recent in vitro investigations have identified the capacity of allicin to activate macrophage activity (Ghazanfari et al 2006) and inhibit macrophage apoptosis (Cho et al 2006). Allicin has also been found to significantly enhance the effect of amphotericin B against *Candida albicans* in vitro and in vivo, mediated through oxidative damage to *C. albicans* (An et al 2008).

Ajoene, another important antimicrobial constituent, has been attributed to more biological activities in vitro and in vivo, including antifungal and antiparasitic actions (Ledezma & Apitz-Castro 2006) with greater antiviral activity than that of allicin, according to one in vitro test (Weber et al 1992).

The role of garlic in oral hygiene and the pathogenesis of dental disease has been investigated. All isolates of *Streptococcus mutans* identified in human carious teeth were sensitive to garlic extract, suggesting a role for garlic in mouthwashes for the prevention of dental caries (Fani et al 2007). This antimicrobial effect against Streptococci was found to continue for 2 weeks post treatment (Groppo et al 2007). Garlic extract was also found to significantly kill *P. gingivalis* and its protease enzymes, indicating a role in the treatment of periodontitis (Bakri & Douglas 2005). A randomised trial of 56 patients found garlic paste to be as effective as that of clotrimazole solution in suppressing signs of oral candidiasis (Sabitha et al 2005).

Helicobacter pylori infection

Several in vitro and in vivo tests have shown that garlic has activity against *H. pylori* (Chung et al 1998, Jonkers et al 1999, O'Gara et al 2000); however, results from clinical studies are equivocal. Two studies found that a combination of garlic and omeprazole produced synergistic effects against *H. pylori* (Cellini et al 1996, Jonkers et al 1999). Recently, rapid anti-*H. pylori* action of garlic oil was observed in artificial gastric juice, suggesting it as a useful treatment (O'Gara et al 2008).

Antineoplastic and chemopreventative effects

Garlic was first used over 3500 years ago in Egypt for the treatment of cancer. Garlic, and, in particular, its OSCs, including allicin, DAS, DADS, DATS and ajoene, have been investigated for their chemoprotective actions (Shukla & Kalra 2007). Recent review articles have identified the multiple mechanisms by which garlic's compounds exert anticarcinogenic properties.

Garlic OSCs demonstrate a capacity to modulate detoxification enzyme systems often responsible for the activation of carcinogens (Yang et al 2001); for example, DAS and its metabolites have been found to competitively inhibit the metabolism of cytochrome P450 2E1 substrates in vitro (Brady et al 1991). This inhibitory activity has been shown in rat nasal mucosa (Hong et al 1991) and hepatocytes (Brady et al 1991).

In addition, garlic OSCs increase the expression of phase II enzymes by enhancement of detoxification of activated carcinogenic intermediates such as quinine reductase and glutathione transferases (Bianchini & Vainio 2001, Rose et al 2005). Phase II enzyme modulation by OSCs has been reported in forestomach and lung cancer in mice (Singh et al 1998), and hepatoma cells (Chen et al 2004). Further investigations have established garlic OSCs' capacity to up-regulate gene expression of glutathione S-transferase.

Garlic OSCs have been shown to suppress neoplastic cell formation by inhibition of cell cycle progression, leading to cellular accumulation in the G2/M phase (Frantz et al 2000, Zheng et al 1997). Human colon cancer cells treated with DADS have not only been seen to arrest the G2/M phase, concomitant alterations were also seen to DNA repair and cellular adhesion factors (Knowles & Milner 2003), with increases in cyclin B1 expression and p53 expression leading to cellular apoptosis (Jo et al 2008, Song et al 2009). Treatment with DATS was reported to be more effective in arresting the G2/M phase of the cell cycle than DADS or DAS in human prostate cells (Xiao et al 2005).

Treatment with garlic and its compounds has been shown to display characteristics of mitotic arrest, exhibiting alterations to tubulin network and chromatin condensation (Herman-Anstosiewicz & Singh 2005). Treatment of human colon cells with garlic-derived compound s-allylmercaptocysteine (SAMC) resulted in depolymerisation of microtubules and cytoskeleton disruption (Xiao et al 2005). Similarly, DATS treatment induced rapid microtubule disassembly and cell cycle arrest in human colon cancer cells (Hosono et al 2008).

Garlic and its constituents have demonstrated actions that modify apoptopic pathways mostly through regulation of antiapoptotic Bcl-2 and pro-apoptotic Bax and Bac proteins (Herman-Antosiewicz et al 2007). For example, modification to transcription ratios of Bax/Bc1-2 proteins following treatment with OSCs has induced apoptosis in neuroblastoma and lung cancer cells (Hong et al 2000), breast cancer cell lines (Nakagawa et al 2001) and prostate cancer cells (Xiao et al 2004). Other mechanisms shown to induce

cellular apoptosis following treatment with OSCs include the induction of reactive oxygen species (ROS) generation (Song et al 2009, Sriram et al 2008), regulation of Akt-Bad (protein kinase B) pathway (Xiao & Singh 2006) and increased free intracellular calcium (Lin et al 2006). Malignant cells appear to be more sensitive to OSC-mediated apoptosis than normal cells (Powolny & Singh 2008).

Garlic OSCs' protective qualities include increased histone acetylation by the inhibition of histone deacetylase (HDAC), leading to cancer cell growth inhibition; for example, treatment of rodent erythroleukaemia and human leukaemia cells with DADS increases H4 and H3 histone acetylations (Lea & Randolph 2001). Increased acetylation has also been reported with treatment of OSCs in human colon cancer cells (Druesne et al 2004) and prostate cancer cells (Arunkumar et al 2007).

Finally, in vitro studies in human and animal cell lines indicate garlic and/or its constituents' ability to inhibit angiogenesis and metastasis. In human colon cancer cells, aged garlic extract was shown to inhibit angiogenesis by reducing endothelial cell motility, inhibiting tube formation, proliferation and invasion (Matsuura et al 2006). Administration of alliin exerted a dose-dependent inhibition of fibroblast growth factor-2-induced human endothelial cell tube formation and angiogenesis (Mousa & Mousa et al 2005). Similarly, treatments with DATS, DADS and DAS have been shown to inhibit capillary-like tube formation, cellular proliferation and migration (Thejass & Kuttan 2007. DADS was also found to inhibit angiogenesis by inhibiting the activation of matrix metalloproteinase (Thejass & Kuttan 2007). In human breast tumour cells, S-allylcysteine (SAC) reduced cell adhesion and invasion through expression of E-cadherin and reduced expression of matrix metalloproteinase (MMP)-2 (Gapter et al 2008). In animal studies, IV administration of ajoene significantly inhibited lung metastasis of melanoma cells (Taylor et al 2006) and aged garlic extract inhibited sarcoma cell migration (Hu et al 2002).

A systematic review published in 2007 suggested that there is consistent scientific evidence derived from animal studies reporting the protective effects of garlic on colorectal cancer (Ngo et al 2007). There are many recently published reviews confirming garlic and its constituents' chemoprotective capacity in various human cancer cell lines (Herman-Antosiewicz et al 2007, Moriarty et al 2007, Nagini 2008, Powolny & Singh 2008, Seki et al 2008, Shukla 2007). It is suggested that future research should focus on pharmacokinetics and pharmacodynamics in humans (Powolny et al 2008).

OTHER ACTIONS

Hepatoprotective effects

Aged garlic extract has a glutathione-sparing effect in the liver and specifically elevates reduced glutathione content, thereby enhancing endogenous protective mechanisms, according to in vitro tests (Wang et al 1999). The protective effects of a single simultaneous dose of garlic oil have been demonstrated on acute ethanol-induced fatty liver in mice, by significantly inhibiting elevation of MDA levels, restoring GSH levels and enhancing SOD, glutathione reductase (GR) and GST activities (Zeng et al 2008).

Homocysteine-lowering action

Aged garlic extract exhibits homocysteine-lowering action that indicates its potential for treatment of cardiovascular disease (Yeh & Yeh 2006). A pilot study conducted in patients with cardiovascular disease showed that pretreatment for 6 weeks with aged garlic extract significantly reduced the effects of acute hyperhomocysteinemia (Weiss et al 2006). It is postulated that the homocysteine-lowering action of aged garlic extract is due to its ability to inhibit CD36 expression and OxLDL uptake in macrophages involved in the formation of atherosclerotic lesions (Ide et al 2006).

Modulates cytochrome P450

Garlic may alter CYP450 enzymes, according to in vitro and animal studies; however, the effect appears unlikely in humans, as clinical studies have not produced the same findings (Dalvi 1992, Foster et al 2001). An in vitro model showed that S-methyl-L-cysteine and S-allyl-L-cysteine (100 micromol/L) produced modest inhibition of CYP3A; however, it is suggested that this would not be the case in vivo (Greenblatt et al 2006). Garlic oil constituent DAS was shown to activate CAR and Nrf2 to induce the drug-metabolising enzymes CYP2B and NAD(P)H quinone oxidoreductase 1 (Fisher et al 2007). In one study, garlic was also shown to have no in vitro inhibiting effects of cytochrome P-450 3A4 (CYP3A4) metabolism (Engdal et al 2009). Recently, an interaction between saquinavir and garlic has been reported, suggestive of a CYP induction effect, but human tests do not support this theory (Piscitelli et al 2002).

Researchers using human volunteers found that garlic oil reduced CYP2E1 activity by 39%, but had no effect on CYP1A2, CYP2D6 or CYP3A4 activity (Gurley et al 2002). The lack of a clinically significant effect on CYP1A2, CYP2D6 and CYP3A4 activity was confirmed in a later study of 12 elderly healthy volunteers receiving garlic oil for 28 days, followed by a 30-day washout period. Garlic oil had a mild inhibitory effect on CYP2E1 activity (by approximately 22%) (Gurley et al 2005). Additionally, tests with allicin also found no effect on CYP 3A4 in women receiving docetaxel treatment (Cox et al 2006).

CLINICAL USE

The use of garlic to treat a variety of conditions is supported by several authorities. Treatment of atherosclerosis, arterial vascular disease, blood lipids, respiratory tract infections and catarrhal conditions has been indicated by The European Scientific Cooperative on Phytotherapy (ESCOP). Treatment of hyperlipidaemia and age-related vascular changes with garlic are supported by the expert

German panel, the Commission E, while the World Health Organisation (WHO) also reports that there is sufficient clinical data to indicate the use of garlic in hyperlipidaemia, age-dependent atherosclerosis and mild hypertension.

Most studies have used a non-enteric coated dehydrated garlic powder preparation standardised to 1.3% alliin content (Kwai, Lichtwer Pharma) or an aged garlic extract (Kyolic, Wakunaga of America).

Cardiovascular disease (CVD)

Epidemiological studies show an inverse correlation between garlic consumption and progression of CVD in general (Rahman & Lowe 2006). A double-blind, placebo-controlled study of 167 patients with hyperlipidaemia demonstrated that Allicor was effective in reducing the 10-year absolute multifactorial risk of cardiovascular diseases (Sobenin et al 2005). Garlic was also found to reduce the 10-year risk of acute myocardial infarction and sudden death in a double-blind, placebo-controlled study of 51 patients with coronary artery disease receiving Allicor for a 12-month period (Sobenin et al 2007).

Hypertension

A meta-analysis of seven clinical trials using a garlic preparation, produced commercially as Kwai, found that three showed a significant reduction in SBP and four in DBP (Silagy & Neil 1994). Kwai was used in these studies in the dosage of 600–900 mg daily. Garlic treatment resulted in a mean reduction in SBP of 7.7 mmHg and 5.0 mmHg in DBP compared with placebo.

In 2000, the Agency for Health Care Research and Quality analysed results from 27 randomised, placebo-controlled trials and reported that results were mixed (Mulrow et al 2000). When significant reductions in blood pressure were observed, these were small.

Several newer trials have since been published, further confirming that the effect on blood pressure is small and sometimes non-significant (Andrianova et al 2002, McMahon & Vargas 1993, Zhang et al 2001a). A recent meta-analysis of 10 clinical trials found that garlic reduces blood pressure in patients with an elevated SBP, but not in those with normal SBP (Reinhart et al 2008). Another meta-analysis of randomised controlled trials with placebo groups, using garlic-only preparations and reporting mean systolic and/or diastolic blood pressure and standard deviations, suggested that garlic preparations are superior to placebo in reducing blood pressure in individuals with hypertension (Ried et al 2008).

Atherosclerosis and arteriosclerosis

Garlic indirectly affects atherosclerosis by reduction of hyperlipidaemia, hypertension and prevention of thrombus formation.

Koscielny et al conducted a randomised, double-blind, placebo-controlled clinical trial involving 152 volunteers to determine whether garlic powder supplements (Kwai 900 mg daily) directly alter plaque volumes in carotid and/or femoral arteries (Koscielny et al 1999). After 4 years' treatment, garlic intake significantly reduced the expected increase in arteriosclerotic plaque volume by 5–18%, with a slight regression also observed. A subsequent re-evaluation of the results found that significant effects were limited to women only (Siegel & Klussendorf 2000).

Hyperlipidaemia

In 2000, a meta-analysis of 13 clinical trials concluded that garlic reduces total cholesterol levels significantly more than placebo; however, the effects can only be described as modest (Stevinson et al 2001). The same year, a systematic review and meta-analysis were published by the Agency for Health Care Research and Quality, which analysed results from 44 studies with lipid outcomes (Mulrow et al 2000). Most studies involved fewer than 100 volunteers and randomisation techniques were unclear in 82% of the studies. Pooled data from the placebo-controlled trials reporting changes in total cholesterol levels found a significant average reduction in total cholesterol levels of 7.2 mg/dL after 4–6 weeks, using any form of garlic, and a reduction of 17.1 mg/dL at 8–12 weeks. Results at 20–24 weeks were not significant and thought to be due to low statistical power, fewer long-term studies or a time-dependent effect of garlic.

Since then, several new studies have been published, with most showing no significant reduction in total cholesterol levels (Gardner et al 2001, Kannar et al 2001, Peleg et al 2003, Turner et al 2004, Zhang et al 2001b, Ziaei et al 2001). In a parallel design trial of 192 patients with LDL cholesterol, treatment with either raw garlic, aged garlic extract or powdered garlic supplement, no significant effects on cholesterol, triglycerides or lipid concentrations were found (Gardner et al 2007). According to one review, non-enteric coated tablets containing dehydrated garlic powder (standardised to 1.3% allicin) produce the most consistent results (Ulbricht & Basch 2005). However, a single-blind, placebo-controlled study of lipid profiles in 150 hyperlipidaemic patients showed that treatment with enteric coated garlic powder (equal to 400 mg garlic, 1 mg allicin) twice daily showed statistically significant decreases in cholesterol and LDL cholesterol, and an increase in HDL cholesterol (Kojuri et al 2007). Moreover, the lipid-lowering effect of time-released garlic powder tablets Allicor (600 mg daily), investigated in a double-blind, placebo-controlled, randomised study of 42 men with mild hypercholesterolaemia, was shown to exert significant reductions in total cholesterol and LDL cholesterol and increased HDL cholesterol as compared to placebo after 8–12 weeks of treatment (Sobenin et al 2008).

Comparative studies

Two clinical studies have compared different garlic preparations with pharmaceutical cholesterol-lowering medicines. Garlic taken as 300 mg three times daily (Kwai) produced similar lipid-lowering effects to 200 mg bezafibrate (a hypolipidaemic fibrate) three times daily in subjects with primary hyperlipidaemia (Holzgartner et al 1992), whereas clofibrate 500 mg was more effective than

an essential oil extract of 50 g raw garlic (Arora & Arora 1981). The administration of 600 mg of fish oil with 500 mg of garlic pearls (garlic oil) per day to 16 hypercholesterolaemic subjects with a total cholesterol above 220 mg/dL for 60 days was found to reduce total cholesterol, LDL, serum triglyceride and very low-density lipoprotein (Jeyaraj et al 2005).

Commission E approves the use of garlic as an adjunct to dietary changes in the treatment of hyperlipidaemia (Blumenthal et al 2000).

Diabetics with hyperlipidaemia

A 12-week, placebo-controlled, single-blind, randomised study of 70 patients with type 2 diabetes and newly diagnosed dyslipidaemia found that treatment with a garlic tablet (Garlex-Bosch Pharmaceuticals: 300 mg, containing 1.3% allicin) twice daily, together with a diet and exercise plan, resulted in a significant reduction in total cholesterol of 28 mg/dL (12.03%) compared to placebo (Ashraf et al 2005). A 12-week, randomised, single-blind, placebo-controlled study of 70 type 2 diabetic patients with newly diagnosed dyslipidaemia demonstrated that garlic (300 mg) twice daily significantly reduced serum total cholesterol and LDL cholesterol and raised HDL cholesterol as compared to placebo (Ashraf et al 2005).

Over a decade ago, one double-blind study reported that 800 mg garlic powder taken daily for a period of 4 weeks reduced blood glucose concentrations by 11.6% (Kiesewetter et al 1993). However, a study using a higher dose of 3 g/day over 26 weeks found no effects (Ali & Thomson 1995).

The metabolic action of Allicor was investigated in a 4-week, double-blind, placebo-controlled study of 60 type 2 diabetic patients, resulting in better metabolic control due to the lowering of fasting blood glucose, serum fructosamine and serum triglyceride levels (Sobenin et al 2008). A review suggests the need for large-scale clinical studies with diabetic patients to elucidate garlic's possible role in prevention and treatment of diabetes (Liu et al 2007).

Antiplatelet effects

Antiplatelet effects of garlic are well recognised, but the dose at which this becomes significant remains uncertain. Results from a 2001 double-blind study have identified a dose of 7.2 g/day of aged garlic extract as significantly inhibiting platelet aggregation and adhesion (Steiner et al 1996).

Peripheral arterial occlusive disease

In 2000, Mulrow et al reported on two double-blind placebo-controlled trials in participants with atherosclerotic lower extremity disease (Mulrow et al 2000). One study of 64 participants showed that pain-free walking distance increased by approximately 40 m with standardised dehydrated garlic (Kwai 800 mg daily), compared with approximately 30 m with placebo over 12 weeks. Cochrane reviewers report that the effect was not significant (Jepson et al 2000). The other study of 100 participants (Mulrow et al 2000) showed that a combination treatment of garlic oil macerate/soya lecithin/hawthorn oil/wheat germ oil significantly increased the maximum walking distance (114%) compared to placebo (17%) ($P < 0.05$).

Infection

Garlic oil is effective against numerous bacteria, viruses and fungi, including *Staphylococcus aureus*, methicillin-resistant *Staphylococcus aureus* (MRSA), and several species of *Candida*, *Aspergillus* and *Cryptococcus neoformans* in vitro (Davis et al 1994, Tsao & Yin 2001, Yoshida et al 1987). As such, it has been used both internally and externally to treat various infections and prevent wound infection.

Tinea pedis, Tinea corporis, Tinea cruris

A trial comparing the effects of three different strengths of ajoene cream (0.4%, 0.6% and 1%) with 1% terbinafine applied twice daily found the cure rate to be 72% for 0.6% ajoene, 100% for 1% ajoene and 94% for 1% terbinafine after 60 days (Ledezma et al 2000).

Vaginitis

Taken internally as a 'natural antibiotic' or applied topically in a cream base, garlic is used to treat vaginitis. The considerable antibacterial activity of garlic provides a theoretical basis for its use in this condition, but controlled studies are not available to determine its effectiveness.

Common cold prevention

A 12-week, double-blind, randomised study involving 146 people demonstrated that allicin-containing garlic preparations significantly reduce the incidence

Clinical Note — Not all garlic preparations are the same

One of the difficulties encountered when interpreting the research available for garlic is comparing the effects of different preparations, which often have not been tested for the presence of important constituents or allicin-releasing potential. It is known that fresh garlic and dried garlic powder contain alliin. When cut, crushed, chewed or dehydrated, the enzyme allinase is rapidly released, which allows the biotransformation of allinin to active organo-sulfur compounds. Some other forms may only contain alliin, and not the necessary alliinase component, thus compromising allicin-releasing potential. An example of the manufacturing process affecting potency has been suggested for a commercial garlic product known as Kwai, which has often been used in cholesterol research (Lawson et al 2001). According to a 2001 experiment, substantial differences were found between tablets manufactured before 1993 (the years when all but one of the positive trials were conducted) and those manufactured after 1993 (the years when all of the negative trials were conducted). Kwai products manufactured after 1993 released only one-third as much allicin as older preparations. Those preparations from before 1993 disintegrated more slowly, protecting alliinase from acid exposure and inactivation.

of colds and accelerate recovery compared with placebo (Josling 2001). More specifically, the number of symptom days in the placebo group was 5.01 compared with 1.52 days in the garlic-treated group. Additionally, garlic reduced the incidence of developing a second cold, whereas placebo did not.

Helicobacter pylori infection

It has been suggested that gastrointestinal lesions, such as gastric ulcers, duodenal ulcers and gastric cancers, are strongly associated with *H. pylori* infection (Scheiman & Cutler 1999). Medical treatment consisting of 'triple therapy' has a high eradication rate; yet, is associated with side effects and has started to give rise to antibiotic resistance. Since garlic intake has been associated with a lowered incidence of stomach cancer, researchers have started investigating whether garlic has activity against *H. pylori*. Several in vitro and in vivo tests have shown garlic to be effective against *H. pylori* (see *Main actions*). However, to date only a few small clinical trials have been conducted, with disappointing and controversial results (Aydin et al 2000, Graham et al 1999, McNulty et al 2001).

A small pilot study of dyspeptic patients with confirmed *H. pylori* infection found that treatment with 4 mg garlic oil capsules taken four times daily with meals for 14 days did not alter symptoms or lead to *H. pylori* eradication (McNulty et al 2001). Another small study using garlic oil 275 mg three times a day (allicin 800 microgram/capsule) either as stand-alone treatment or in combination with omeprazole (20 mg twice daily) found that both treatments produced similar results (Aydin et al 2000). These results were confirmed in another small clinical study (Graham et al 1999).

Protective effects against cancer

A 2001 critical review of the epidemiological evidence suggests a preventive effect for garlic consumption in stomach and colorectal cancers, but not other cancers (Fleischauer & Arab 2001). With regard to gastric cancer protection, case-control studies suggested a protective effect for raw and/or cooked garlic when eaten at least once a week, whereas protective effects against colorectal cancer seem to require at least two servings of garlic per week. A similar view was reported in a 2003 review by Ernst, which stated that the weight of evidence to support the use of allium vegetables, such as garlic, in cancer is clearly positive. However, a recently published review of 19 human studies evaluated the evidence supporting a relationship between garlic intake and a reduction in risk of different cancers with respect to food labelling. No evidence was found to suggest that garlic consumption reduced the risk of gastric, breast, lung or endometrial cancer, with very limited evidence supporting a reduction in risk of colon, prostate, oesophageal, larynx, oral, ovary or renal cell cancers due to garlic consumption (Kim & Kwon 2009).

Intervention study in colorectal cancer

A preliminary double-blind, randomised clinical trial in patients with colorectal adenomas — precancerous lesions of the large bowel — produced promising results with the use of high-dose aged garlic extract (AGE 2.4 mL/day) (Tanaka et al 2006). The study of 51 patients measured the number and size of adenomas at baseline and at 6 and 12 months and found that AGE significantly suppressed both the size and the number of colon adenomas in patients after 1 year of treatment ($P = 0.04$). In comparison, the number of adenomas increased linearly in the control group from the beginning. A systematic review of scientific evidence from all studies conducted over the last decade that examined the effects of garlic on colorectal cancer (CRC) was conducted. One randomised controlled trial (RCT) reported, for CRC patients taking AGE, a statistically significant 29% reduction in both size and number of colon adenomas and a meta-analysis confirmed protective effect, with a 30% reduction in relative risk. Five of eight case-control/cohort studies suggested that high intake of raw/cooked garlic produced a chemoprotective effect. Review of 11 animal studies showed a significant anticarcinogenic effect of garlic. Overall, the authors concluded that there was consistent scientific evidence derived from RCT animal studies, despite heterogeneity of human epidemiological studies (Ngo et al 2007).

Analysis of data from a multicentre, case-control study of 454 endometrial cancer cases and 908 controls found a moderate protective role for allium vegetables on the risk of endometrial cancer, with a significant inverse trend identified for high intakes of garlic (Galeone et al 2008). Topical application of garlic-derived ajoene to tumours of 21 patients with either nodular or superficial basal cell carcinoma resulted in reduction in tumour size in 17 patients. Chemical assays prior to and posttreatment showed a significant decrease in the expression of the apoptosis-suppression protein Bcl-2 (Tilli et al 2003).

OTHER USES

Some early research suggests that garlic may prevent the incidence of altitude sickness (Fallon et al 1998, Kim-Park & Ku 2000) and reduce mosquito numbers (Jarial 2001). It has also been used to assist in heavy metal detoxification. Studies with experimental animal models provide some support for its use in this way (Bone & Morgan 2005).

DOSAGE RANGE

General guide

- Fresh garlic: 2–5 g/day (ensure it is bruised, crushed or chewed).
- Dried powder: 0.4–1.2 g/day.
- AGEs have been studied in amounts ranging from 2.4 to 7.2 g/day.
- Oil: 2–5 mg/day.
- Garlic preparations that will provide 4–12 mg alliin daily.
- Fluid extract (1:1): 0.5–2 mL three times daily.

According to clinical studies

- Hypertension: 600–900 mg/day in divided doses (delivering approximately 5000–6000 microgram allicin potential).
- Hyperlipidaemia: 600–9000 mg/day.

- Fungal infection: topical 0.4–0.6% ajoene cream applied twice daily.
- Occlusive arterial disease: 600–800 mg/day.

It is important to be aware of the thiosulfinate content, in particular allicin-releasing ability, of any commercial product to ensure efficacy.

ADVERSE REACTIONS

Internal use

Breath and body odour, allergic reactions, nausea, heartburn, flatulence, abdominal discomfort and diarrhoea have been reported (Berthold et al 1998). These side effects are more common when garlic is taken on an empty stomach.

Headache, myalgia and fatigue were reported in one study using a dose of 900 mg garlic powder (standardised to 1.3% alliin) (Holzgartner et al 1992).

Topical use

An ajoene 0.6% gel produces a transient burning sensation after application, according to one study (Ledezma et al 1999). Contact dermatitis can occur — one study using patch testing found that 5.2% of volunteers had contact sensitisation (Lembo et al 1991).

SIGNIFICANT INTERACTIONS

Saquinavir and ritonavir

A clinical study showed that garlic powder reduced blood levels of saquinavir and ritonavir due to stimulation of P450 isoenzymes, and therefore may reduce efficacy of drug — avoid using concurrently (Piscitelli et al 2002). However, in a clinical study of 10 participants, 10 mg of odourless garlic had no significant effect on the pharmacokinetics of ritonavir (Gallicano et al 2003).

Anticoagulants

Theoretically, a pharmacodynamic interaction is possible when using garlic at high doses (> 7 g), in excess of usual dietary amounts; however, results from clinical studies cast doubt on this proposition. Published clinical studies have identified no significant action of enteric-coated or aged garlic on warfarin pharmacodynamics or pharmacokinetics. A double-blind, randomised, placebo-controlled pilot study of 48 patients demonstrated that the concomitant use of garlic containing 14.7 mg/day of *S*-allylcysteine and warfarin showed no adverse effects (Macan et al 2006). An open-label, three-treatment, randomised, crossover clinical trial involving 12 healthy males, investigating potential effects of garlic and cranberry on warfarin (25 mg single dose), found that two garlic tablets daily containing 2000 mg of fresh garlic bulb equivalent to 3.71 mg of allicin per tablet did not significantly alter warfarin's pharmacokinetics or pharmacodynamics (Mohammed Abdul et al 2008). Use caution with doses > 7 g/day.

Antiplatelet drugs

Theoretically, a pharmacodynamic interaction is possible when using garlic at high doses in excess of usual dietary amounts, although a small clinical study involving 10 adult participants showed garlic had no effect on platelet function (Beckert et al 2007). Observe.

Antihypertensive agents

Theoretically, potentiation effects are possible when using garlic at high doses in excess of usual dietary amounts — this can be used as adjunctive therapy to produce beneficial results.

Antihyperlipidaemic agents

Theoretically, potentiation effects are possible when using garlic at high doses in excess of usual dietary amounts — this can be used as adjunctive therapy to produce beneficial results — observe.

Helicobacter pylori triple therapy

Additive effects are theoretically possible. While it is prudent to observe the patient for adverse reactions, the interaction may be beneficial.

Hepatotoxic drugs

Garlic may exert hepatoprotective activity against liver damage induced by drugs, according to in vitro tests, which suggests a beneficial interaction.

Paracetamol

In vivo protection from garlic and ajoene on paracetamol-induced hepatotoxicity has been observed (Hsu et al 2006) — beneficial interaction.

CONTRAINDICATIONS AND PRECAUTIONS

Patients with bleeding abnormalities should avoid therapeutic doses of garlic. Although usual dietary intakes are likely to be safe prior to major surgery, suspend the use of high-dose garlic supplements 1 week before, as there is a theoretical increased risk of bleeding.

If being used as part of a topical application, a test patch is advised before more widespread application.

PRACTICE POINTS/PATIENT COUNSELLING

- Garlic is both a food and a therapeutic medicine capable of significant and varied pharmacological activity.
- It has antioxidant, antimicrobial, antiplatelet, antithrombotic, antihypertensive, lipid-lowering, anti-atherosclerotic and vasoprotective activities.
- It also enhances microcirculation and may have hypoglycaemic, anti-inflammatory and immunostimulant activities.
- Garlic is used as a treatment for many common infections, to reduce the incidence of colds, to improve peripheral circulation and to manage hyperlipidaemia and hypertension.
  - Topical garlic preparations have been used to treat common fungal infections.
- Increased consumption of garlic has been associated with a decreased risk of stomach and colorectal cancers, according to a review of the epidemiological evidence.
- Several important drug interactions are possible with garlic (refer to significant interactions).

PREGNANCY USE

Garlic is not recommended at doses greater than usual dietary intakes.

PATIENTS' FAQs

What will this herb do for me?

Garlic has many different actions in the body and is used to treat conditions such as elevated blood pressure, cholesterol levels, poor peripheral circulation and common infections such as the common cold, flu and athlete's foot. Research suggests that it may be effective in all of these conditions; however, in some cases, the effect is small.

When will it start to work?

This varies greatly, depending on the reason for use. For example, garlic has been shown to improve microcirculation within 5 h of ingestion, whereas slowing down of the atherosclerotic process or cancer-protective effects are likely to require several years' continuous use.

Are there any safety issues?

When garlic is taken at doses above the usual dietary levels, it may interact with a number of medications. Also, it should not be taken by people with bleeding disorders.

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Gentian

HISTORICAL NOTE The genus *Gentiana* is derived from Gentius, king of ancient Ilyra who is attributed with the discovery of its therapeutic effects (Blumenthal 2000). In ancient Greece and Rome it was used to relieve common gastrointestinal symptoms, much as it is used today. It was first noted in the Chinese medical literature in 50 BC (Willard 1991).

OTHER NAMES
Gentiana, yellow gentian, wild gentian

BOTANICAL NAME/FAMILY
Gentiana lutea (family Gentianaceae)

PLANT PARTS USED
Root and rhizome

CHEMICAL COMPONENTS
Secoiridoid bitter glycosides, oligosaccharides, phenolic acids, phytosterols, polysaccharides (inulin and pectin), tannin, lupeol, beta-amyrin triterpenes, xanthones and essential oil. Analysis of several commercially available *G. lutea* samples showed that gentiopicroside is the most prevalent bioactive compound (4.46–9.53%), followed by loganic acid (0.10–0.76%), swertiamarin (0.21–0.45%) and the xanthone glycosides. Gentisin and isogentisin were found in much lower concentrations between 0.02 and 0.11%, respectively (Aberham et al 2007).

MAIN ACTIONS
The active principals in gentian root are the bitter constituents, gentiopicroside and amarogentin.

Digestive stimulant
The bitter principals induce reflex excitation of taste receptors and increased saliva, gastric juice and bile secretion thereby stimulating appetite and digestion according to in vivo experiments. The small human study confirmed that oral administration of gentian root extract increases gastric juice secretion and emptying of the gall bladder (ESCOP 2003).

Antioxidant
This has been demonstrated in vivo (Amin 2008).

Promotes wound healing
The gentiopicroside, sweroside and swertiamarine constituents from *Gentiana lutea* demonstrate wound healing properties in animal models, which seems to be mainly due to increased stimulation of collagen production and mitotic activity (Ozturk et al 2006).

OTHER ACTIONS
A gentian root preparation inhibited *Helicobacter pylori* in vitro (Mahady et al 2005).

Antioxidant activity has been observed in vitro for the ethyl acetate and chloroform fractions of gentian (Calliste et al 2001). Animal studies with amarogentin have identified antileishmanial properties (Medda et al 1999). An orally administered crude extract of *Gentiana lutea* (1 g/kg b wt/day) prevented both the reproductive toxicity and oxidative damage induced in rat testes in response to a high acute dose of ketoconazole.

Traditionally, gentian is considered to have stomachic, anthelmintic, antiseptic, anti-inflammatory and tonic activity (Willard 1991).

CLINICAL USE
Gentian root preparations have not been significantly investigated under clinical trial conditions, so evidence is mainly derived from traditional, in vitro and animal studies. It is a popular remedy amongst naturopaths and herbalists.

Dyspepsia and flatulence
The considerable bitter taste of gentian provides a theoretical basis for its use in dyspepsia and flatulence for which increased saliva and gastric acid secretion would be beneficial. Commission E and ESCOP approve its use for this indication (Blumenthal 2000, ESCOP 2003).

Loss of appetite
The considerable bitter taste of gentian provides a theoretical basis for its use in anorexia when increased saliva and gastric acid secretions would be beneficial. Commission E and ESCOP approve its use for this indication (Blumenthal 2000, ESCOP 2003).

OTHER USES
Traditionally, gentian has also been used for gout, amenorrhoea, diarrhoea and worms in the stomach and bowel (Willard 1991). Gentian is also used in

Clinical note — Herbs in alcoholic drinks
The maceration of herbs and spices in wine was common practice in antiquity, and the invention of aromatised wine, the ancestor of vermouth, has been attributed to Hippocrates (Liddle & Boero 2003). Herbs are still commonly used in alcoholic drink production today, either as flavourings, or as both fermentation substrates and flavouring agents. The volatile components of a herb will provide its distinctive odour, whereas non-volatile constituents can affect some gustatory reactions and produce a physiological effect. Bitter herbs such as gentian are used for flavour, but also because they contain a significant amount of fermentable sugars that can be converted by strains of yeast into ethanol in an alcoholic fermentation process. Examples of other herbs that are used in brandies, flavoured spirits, liqueurs, medicinal wines and vermouth are anise, caraway, cardamom, coriander, dandelion, sage and yarrow (Veljkovic & Stankovic 2003).

alcoholic drinks such as brandy, medicinal wines and vermouth.

DOSAGE RANGE

General guide

- Cut root or dried extract: 2–4 g/day.
- Fluid extract (1:1): 1–2 mL taken 1 hour before meals up to three times daily.
- Tincture (1:5): 3–12 mL/day.
- Infusion: 1–2 g in 150 mL boiled water taken 1 hour before meals and up to three times daily.

ADVERSE REACTIONS

Headaches have been reported (ESCOP 2003) and nausea and vomiting with high doses.

SIGNIFICANT INTERACTIONS

Interactions are unknown.

CONTRAINDICATIONS AND PRECAUTIONS

Contraindicated in gastric or duodenal ulcers and hyperacidity according to Commission E (Blumenthal 2000).

PREGNANCY USE

There is insufficient reliable information available to make a recommendation.

PRACTICE POINTS/PATIENT COUNSELLING

- Gentian root and its preparations are extremely bitter.
- Gentian preparations stimulate salivation, gastric juice and bile secretion.
- They are used to improve digestion, relieve flatulence and stimulate appetite.
- Little clinical investigation has been undertaken with the herb, so evidence of efficacy relies on traditional and animal studies.
- It should not be used in cases of gastric or duodenal ulcer or hyperacidity.

PATIENTS' FAQs

What will this herb do for me?

Gentian preparations stimulate taste buds when taken orally, and increase gastric juice secretion, thereby improving digestion.

When will it start to work?

Effects are expected within several minutes of ingestion.

Are there any safety issues?

It should not be used by people with gastric or duodenal ulcers or with gastric hyperacidity.

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Ginger

HISTORICAL NOTE Ginger has been used as both a food and a medicine since ancient times. Confucius wrote about it in his Analects, the Greek physician, Dioscorides, listed ginger as an antidote to poisoning, as a digestive, and as being warming to the stomach in De Materia Medica, and the Koran, the Talmud and the Bible all mention ginger. Records suggest that ginger was highly valued as an article of trade and in 13th and 14th century England, one pound of ginger was worth the same as a sheep (Rosengarten 1969). Ginger is still extremely popular in the practice of phytotherapy, particularly in traditional Chinese medicine (TCM), which distinguishes between the dried and fresh roots. It is widely used to stimulate circulation, treat various gastrointestinal disorders and as a stimulant heating agent.

OTHER NAMES

African ginger, Indian ginger, Jamaica ginger, common ginger, rhizoma zingiberis, shokyo (Japanese).

BOTANICAL NAME/FAMILY

Zingiber officinale Roscoe (family Zingiberaceae)

PLANT PART USED

Rhizome

CHEMICAL COMPONENTS

The ginger rhizome contains an essential oil and resin known collectively as oleoresin. The composition of the essential oil varies according to

the geographical origin, but the chief constituents, sesquiterpene hydrocarbons, which are responsible for the characteristic aroma, are fairly constant.

The oleoresin contains:

- Sesquiterpenes: zingiberene, ar-curcumene, beta-sesquiphellandrene and beta-bisabolene.
- Pungent phenolic compounds: gingerols and their corresponding degradation products, shogaols, zingerone and paradol. Zingerone and shogaols are found in small amounts in fresh ginger and in larger amounts in dried or extracted products (Govindarajan 1982).
- Other constituents: diarylheptanoids galanolactone (diterpenoid), 6-gingesulfonic acid, monoacyldigalactosylglycerols (Awang 1992, Bhattarai et al 2001, Charles et al 2000, Govindarajan 1982, Kikuzaki et al 1991, WHO 2003, Yamahara et al 1992, Yoshikawa et al 1992, 1993).

MAIN ACTIONS

Anti-emetic

Ginger has demonstrated anti-emetic activity in both experimental models and human studies. It appears that several key constituents are responsible which exert several different mechanisms. In vivo studies have demonstrated [6]-, [8]- and [10]-gingerol as well as [6]-shogaol exert anti-emetic activity (Kawai et al 1994, Abdel-Aziz et al 2006), most likely by acting on the 5-HT(3) receptor ion-channel complex either by binding directly to a modulatory site distinct from the serotonin binding site or indirectly via underlying muscarinic receptors. Specific constituents of ginger volatile oil including terpinolene, beta-pinene and alpha-phellandrene were also found to induce an anti-spasmodic effect via interaction with the 5-HT(3) receptor channel system in rat ileum (Riyazi et al 2007). Galactone has also been identified as a serotonin-receptor antagonist (Huang et al 1991, Mustafa et al 1993, Yamahara et al 1990). Such mechanisms of action also explain the inhibitory effect of ginger on serotonin-induced diarrhoea and antispasmodic effect on visceral and vascular smooth muscle.

Ginger has been shown to blunt gastric dysrhythmias and nausea evoked by acute hyperglycaemia in humans. The anti-arrhythmic and anti-emetic effects are thought to be due to a blockade of prostaglandins rather than inhibition of their release (Gonlachanvit 2001. Ginger has also been shown to reduce radiation-induced gastrointestinal distress and emesis in rat models, which is thought to be due at least in part to its antioxidant properties and the ability to scavenge free radicals and inhibit lipid peroxidation (Sharma et al 2005). Ginger extract displayed comparable radioprotection against radiation-induced taste aversion (CTA) when compared to dexamethasone and ondansetron in male and female rats. The most effective concentration was 1000 microgram/mL of ginger extract, which exerted free radial scavenging of hydroxyl ions and nitric oxide and modulation of CTA (Haksar et al 2006).

Gastrointestinal activity

Ginger exerts several effects in the gastrointestinal tract, which lead to an improvement in gastrointestinal symptoms. It stimulates the flow of saliva, bile and gastric secretions (Platel & Srinivasan 1996, 2001, Yamahara et al 1985) and has been shown to increase gastrointestinal motility in several animal models and human studies (Gupta & Sharma 2001, Micklefield et al 1999, Phillips et al 1993). In a recent randomised double-blind study involving 24 healthy volunteers, ginger was found to accelerate gastric emptying and stimulate antral contractions (Wu et al 2008). Ginger has also been observed to have prokinetic activity in mice in vivo and anti-spasmodic activity in vitro (Ghayur & Gilani 2005). These findings appear to support the traditional use of ginger in the treatment of gastrointestinal discomfort, colic, diarrhoea and bloating and its use as a carminative agent. Further in vitro studies confirm cholinergic agonistic activity on postsynaptic M3 receptors, as well as suggesting an inhibitory effect on presynaptic muscarinic autoreceptors (Ghayur et al 2007). The [6]-gingerol constituent displayed the strongest antispasmodic activity (Ghayur et al 2008).

Anti-ulcer activity

A number of in vivo studies have identified anti-ulcer activity for ginger extract and several of its isolated constituents. The orally administered acetone extract of ginger at a dose of 1000 mg/kg and zingiberene, the main terpenoid in this extract, at 100 mg/kg significantly inhibited gastric lesions by 97.5% and 53.6%, respectively. Additionally, the pungent principle, [6]-gingerol at 100 mg/kg, significantly inhibited gastric lesions by 54.5%. These results suggest that both zingiberene and [6]-gingerol are important constituents responsible for ginger's anti-ulcer activity (Yamahara et al 1988). Other constituents demonstrating anti-ulcer properties in gastric ulcer models in rats include beta-sesquiphellandrene, beta-bisabolene, ar-curcumene and shogaol (Sertie et al 1992, Yoshikawa et al 1994).

Helicobacter pylori has been identified as a major causative factor in gastric ulcer. In vitro studies have established ginger extract containing gingerols effectively inhibited the growth of 19 strains of *H. pylori* including CagA+ strains (Mahady et al 2003, 2005). While ginger is effective in inhibiting *H. pylori*, its ability to prevent bacterial adhesion to the stomach tissue is limited (O'Mahoney et al 2005).

In addition to direct anti-ulcer activity, ginger exerts synergistic effects with the antibiotic clarithromycin in inhibiting different *H. pylori* isolates independent of the organisms' susceptibility to clarithromycin (Nostro et al 2006). Ginger-free phenolic and ginger hydrolysed phenolic fractions were found to be potent inhibitors of gastric cell proton potassium ATPase and *H. pylori*, exhibiting a six-to-eight-fold better potency over lansoprazole (Siddaraju & Dharmesh 2007).

Hypolipidaemic

Ginger demonstrates significant lipid lowering activity in several animal models and, more recently, a double-blind clinical trial.

High doses of an aqueous extract of ginger (500 mg/kg) significantly reduced serum cholesterol according to an animal study that used oral doses of a raw aqueous extract of ginger administered daily for a period of 4 weeks (Thomson et al 2002). Treatment with ginger methanol and ethyl acetate extracts (250 mg/kg) for 8 weeks also resulted in a significant reduction in lipid levels in vivo (Goyal & Kadnur 2006). Similarly, methanolic and ethyl acetate extracts of dried ginger rhizome significantly reduced fructose elevated lipid levels and body weight in vivo (Kadnur & Goyal 2005). Reductions in lipid levels were further reported for ethanolic extract of ginger (200 mg/kg for 20 days) by using a streptozocin-induced diabetic rat model. In addition, herbal treatment effectively reduced serum glucose (Bhandari et al 2005).

Effects on triglyceride levels are more difficult to determine, as one study demonstrated that 250 microgram ginger extract/day reduced serum triglyceride levels by 27% in mice (Fuhrman et al 2000), whereas another study using a high dose of 500 mg/kg found no significant effects (Thomson et al 2002).

An ex vivo study found that 250 microgram/day of a standardised ginger extract significantly reduced plasma cholesterol, triglycerides and LDL cholesterol levels, the LDL basal oxidative state, as well as LDL cholesterol and serum cholesterol's susceptibility to oxidation and aggregation, compared with placebo. Ginger also reduced aortic atherosclerotic lesions by 44% in atherosclerotic mouse aorta (Fuhrman et al 2000).

According to a double-blind controlled clinical trial study of 85 volunteers, ginger (3 g/day) demonstrates clinically significant lipid lowering effects compared to controls. After 45 days of treatment, triglyceride and cholesterol levels were reduced as well as a reduction in LDL levels and an increase in HDL levels (Alizadeh-Navaei et al 2008).

Glycaemic response

Tests conducted with various animal models indicate hypoglycaemic activity for ginger.

One study tested 500 mg/kg of raw ginger administered to streptozotocin-induced diabetic rats, which proved to significantly lower serum glucose. Treatment with ginger also resulted in a significant reduction in proteinuria, enuresis, thirst and sustained maintenance of initial weights (Al-Amin et al 2006).

Researchers postulate that ginger improves insulin sensitivity resulting in a reduction in elevated glucose levels (Goyal & Kandur 2006). The results of one in vivo study suggest that ginger is insulinotropic rather than hypoglycaemic (Islam & Choi 2008).

Gingerols have been identified as the main constituent group responsible for improving insulin sensitivity. In an assay for aldose reductase inhibitors within ginger, five active compounds were isolated and two were found to be inhibitors of recombinant human aldose reductase (Kato et al 2006).

Anti-inflammatory and analgesic

The anti-inflammatory and analgesic effects reported for ginger are attributed to multiple constituents exerting several different mechanisms.

An acetone extract containing gingerols, shogaols and minor compounds like gingerenone A, [6]-gingerdiol, hexahydrocurcumin and zingerone have been shown synergistically to produce dose-dependent anti-inflammatory effects (Schuhbaum & Franz 2000). Other studies have identified the gingerols and diarylheptanoids and gingerdione as the key compounds responsible (Flynn et al 1986, Kiuchi et al 1992).

Investigations on macrophages in vitro found that [6]-shogaol and [6]-gingerol inhibit the expression of inflammatory iNOS and COX-2 proteins (Pan et al 2008). [6]-Gingerol has also been shown to inhibit catalytic activity of iNOS in murine macrophages via attenuation of NF-kappaB-mediated iNOS gene expression (Aktan et al 2006). [6]-Gingerol proved to be useful in treatment of inflammation by selectively inhibiting the production of inflammatory cytokines of murine peritoneal macrophages without interfering with the antigen presenting function of the macrophages (Tripathi et al 2007). Ginger extract inhibited interleukin (IL)-12, tumour necrosis factor (TNF)-alpha, IL-1-beta in lipopolysaccharide-stimulated macrophages and significantly reduced T-cell proliferation (Tripathi et al 2008).

Ginger has been found to modulate the arachidonic acid cascade, as COX-1 and -2 and lipoxygenase inhibition has been shown in vitro (Kobayashi et al 1987) and high oral doses of an aqueous extract of ginger (500 mg/kg) significantly lowered serum PGE2 and thromboxane B2 levels in rats (Thomson et al 2002). A hydroalcoholic extract of ginger exerted anti-inflammatory and attenuated COX metabolites in rat trachea hyperactivity for 90 minutes and 48 hours after exposure to lipopolysaccharide (LPS). Ginger reduced serum levels of prostaglandin (PGE2) and thromboxane (TXA2) post LPS exposure (Aimbire et al 2007). Ginger also suppresses leukotriene biosynthesis by inhibiting 5-lipoxygenase, thus distinguishing ginger from non-steroidal anti-inflammatory drugs (NSAIDs). Additionally, ginger extract has been shown to inhibit thromboxane synthase (Langner et al 1998) and a ginger extract (EV.EXT 77) has been found to inhibit the induction of several genes involved in the inflammatory response. These include genes encoding cytokines, chemokines and the inducible enzyme COX-2, thus providing evidence that ginger modulates biochemical pathways activated in chronic inflammation (Grzanna et al 2005).

Gingerol and [8]-gingerol have been found to evoke capsaicin-like intracellular Ca^{2+} transients and ion currents in vitro and it has been suggested that gingerols represent a novel class of naturally occurring vanilloid receptor agonists that contribute to ginger's medicinal properties (Dedov et al 2002). This is supported by the finding that topical application of ginger creams or compresses produce an analgesic capsaicin-like effect on the release of the immunoreactive substance P from primary afferent neurons (Onogi et al 1992). In an animal study of chemically induced inflammation, ginger

extract reduced oedema that was partly caused by serotonin-receptor antagonism (Penna et al 2003). Additionally, ginger oil has shown anti-inflammatory activity, significantly suppressing both paw and joint swelling in severe adjuvant arthritis in rats (Sharma et al 1994).

In an animal model of rheumatoid arthritis both crude ginger extract and gingerols were efficacious in preventing streptococcal cell wall-induced arthritis. However, the crude ginger extract, which also contained essential oils, was more effective in preventing both joint inflammation and attenuating cellular destruction (Funk et al 2009).

Antiplatelet

It has been suggested that gingerols and their derivatives represent a potential new class of platelet activation inhibitors, with synthetic gingerols being found to inhibit the arachidonic acid-induced platelet release reaction in vitro in a similar dose range as aspirin possibly due to an effect on COX activity in platelets (Koo et al 2001, Lu 2005, Nurtjahja-Tjendraputra et al 2003, Tjendraputra et al 2001).

Powdered ginger exerted an antiplatelet activity when taken in very high doses of at least 10 g, according to one human study (Bordia et al 1997). A randomised double-blind study found that doses up to 2 g of dried ginger had no effect on bleeding time, platelet aggregation or platelet count (Lumb 1994). This lack of effect has been demonstrated in healthy volunteers (Janssen et al 1996) and those with type 1 diabetes mellitus or coronary artery disease (Bordia et al 1997).

Antimicrobial and antiparasitic

Ginger extract, several of its main constituents and essential oil of ginger exhibit antimicrobial activity in vitro and in vivo. Ginger extract has been shown to have an antibacterial effect against *Staphylococcus aureus*, *Streptococcus pyogenes*, *Streptococcus pneumoniae* and *Haemophilus* collected from throat swaps of infected individuals. The minimum inhibitory concentration of ginger ranged from 0.0003 to 0.7 microgram/mL, and the minimum bactericidal concentration ranged from 0.135 to 2.04 microgram/mL (Akoachere et al 2002). The anti-*H. pylori* effects of ginger have also been shown to inhibit *H. pylori* CagA+ strains in vitro (Mahady et al 2003). Essential oils of ginger have also been shown to have antimicrobial activity against gram-positive and gram-negative bacteria in vitro (Martins et al 2001).

Ginger constituents

[10]-Gingerol and [12]-gingerol successfully inhibited oral bacteria associated with periodontitis. Ethanol and *n*-hexane extracts of ginger have demonstrated antibacterial activities against the bacteria *Porphyromonas gingivalis*, *Porphyromonas endodontalis* and *Prevotella intermedia*, associated with periodontal disease effectively inhibited the growth of these anaerobic gram-negative bacteria (Park et al 2008). Intraperitoneally administered ginger exerted a dose-dependent antimicrobial activity against *Pseudomonas aeruginosa*, *Salmonella typhimurium*, *Escherichia coli* and *Candida albicans* (Jagetia et al 2003).

Gingerols demonstrated antibacterial activity against *Bacillus subtilis* and *Escherichia coli* in vitro (Yamada et al 1992). [10]-Gingerol was found to potentiate the antibacterial actions of aminoglycosides in vancomycin-resistant enterococci, bacitracin and polymixin B suggesting [10]-gingerol increases membrane permeability of enterococcal cells promoting an enhanced influx of aminoglycosides (Nagoshi et al 2006).

Ginger has also shown antischistosomal activity. Gingerol (5.0 ppm) completely abolished the infectivity of *Schistosoma* spp (blood flukes) in animal studies (Adewunmi et al 1990). Gingerol and shogaol exhibited potent molluscicidal activity in vivo. Shogaol and gingerol have demonstrated antinematode activities; 6.25 microgram/mL 6-shogaol destroyed *Anisakis* larvae within 16 hours in vitro, whereas the anti-nematodal medication pyrantel pamoate had no lethal effect at 1 mg/mL (Goto et al 1990).

Antifungal and antiviral

Ginger constituents have demonstrated antifungal and antiviral activity. Shogaol and zingerone strongly inhibited *Salmonella typhi*, *Vibrio cholerae* and *Tricophyton violaceum*. Aqueous extracts have also been shown to be effective against *Trichomonas vaginalis* (Henry & Piggott 1987). Several sesquiterpenes, but especially beta-sesquiphellandrene, isolated from ginger have also been shown to have antirhinoviral activity in vitro (Denyer et al 1994).

Essential oils of ginger have been shown to have activity yeasts and filamentous fungi in vitro (Martins et al 2001). Such oils have exhibited virucidal activity against acyclovir-sensitive and resistant strains of herpes simplex-1 reducing plaque formation significantly (Schnitzler et al 2007). A further in vitro study has indicated a dose-dependent virucidal activity against herpes simplex-2 is possible by interaction with the viral envelope (Koch et al 2008).

Antioxidant

Clinical investigations have confirmed that ginger displays strong in vitro and in vivo antioxidant properties. Orally administered ginger significantly lowered levels of free radicals and raised the activities of endogenous antioxidants, superoxide dismutase and catalase and had a sparing effect on vitamins C and E (Jeyakumar et al 1999). Ginger has been found to protect against lipid peroxidation in the liver (Ahmed et al 2008) and kidney (Asani & Verma 2007). An in vivo and in vitro research has proved [6]-gingerol to be effective in reducing ultraviolet B (UVB)-induced intracellular reactive oxygen species (ROS), UVB-induced expression of COX-2 and inhibited the translocation of NF-kappaB from cytosol to cell nucleus. Moreover, topical application of [6]-gingerol prior to UVB exposure on hairless mice inhibited COX-2 mRNA, and protein and NF-kappaB translocation (Kim et al 2007).

Immunomodulation

In vitro and in vivo research suggests that ginger extract exerts some degree of immunomodulatory activity (Ahui et al 2008, Imanishi et al 2006, Tripathi et al 2008).

Ginger exerted an immunosuppressive in vitro lymphocyte proliferation analysis, an effect modulated through IL-2 production (Wilasrusmee et al 2002). Ginger oil has also been shown to have immunomodulatory activity in mice, with dose-dependent inhibition of T lymphocyte proliferation and IL-1-alpha secretion and reduced delayed type of hypersensitivity response in vivo (Zhou et al 2006).

Hepatoprotective

Ginger has significant hepatoprotective effects comparable to those of silymarin, according to a research with experimental models of alcohol-induced liver damage (Bhandari et al 2003). The effect appears to be mediated by an antioxidative mechanism. Reversal of ethanol-induced liver damage was achieved following the treatment with 1% ginger for 4 weeks. The hepatoprotective action was mediated by preventing a decline in antioxidant status (Mallikarjuna et al 2008). Pretreatment with an ethanol extract of ginger exerted a protective effect against carbon tetrachloride and acetaminophen induced acute liver damage in rats, with attenuation of serum and liver marker enzymes (Yemitan & Izegbu 2006). In a similar study ginger exerted significant declines in the activities of serum transaminases and alkaline phosphatase and restoration of hepatic oxidative status post administration of a single dose (Ajith et al 2007).

Nephroprotection

Ginger prevented the decline in renal antioxidant status by increasing glutathione-s-transferase activity in an experimental model of nephrotoxicity (Ajith et al 2008). Ginger exhibited a significant dose-dependent nephroprotective role in experimentally induced acute renal damage when administered as a stand-alone treatment (250 mg/kg) and when used in combination with vitamin E (Ajith et al 2007).

Chemoprotective

The inhibitory effects of ginger in tumour development have been demonstrated in animal models and human cell lines. Antitumour properties have been isolated to several key constituents of ginger including [6]-gingerol, [6]-paradol, shogaols, zerumbone and zingerone and are partly due to an antioxidative and anti-inflammatory mechanism (Kim et al 2005).

Application of ginger or its constituents achieved induction of apoptosis in cancerous cells resulting in suppression of proliferation (Lee & Surh 1998) and apoptosis resulting in cell transformation (Bode et al 2001). The apoptotic effect of ginger constituents was also demonstrated in human promyelocytic leukaemia cells (Wei et al 2005). The modulation of proteins involved in apoptosis has also been demonstrated in vivo and in vitro prostate cancer models (Shukla et al 2007). [6]-Gingerol administration exerted actions of cell cycle arrest and induction of apoptosis in suppression of hepatoma cells (Yagihashi et al 2008). [6]-Gingerol was also found to exert a direct suppressive effect on colon cancer cell growth and inhibit angiogenesis by reduction in tumour blood supply (Brown et al 2008). [6]-Shogaol has been found to effectively induce apoptotic cell death in human hepatoma p53 mutant cells by way of an intracellular oxidative stress mediated cascade which ultimately leads to cell death (Chen et al 2007).

Reduction of lipid peroxidation and increased antioxidant activity was attributed to suppression of colon carcinogenesis by ginger in male Wistar rats (Manju & Nalini 2005). Differing types of tumours exhibit high NF-kappaB activity sustaining angiogenesis and cell proliferation gingerols were found to display properties inhibiting the activation of NF-kappaB (Kim et al 2009, Takada et al 2005).

Human cell studies show that ginger and its constituents have a potential therapeutic role in the treatment and prevention of human breast cancer (Lee et al 2008), ovarian cancer (Rhode et al 2007), gastric cancer (Ishiguro et al 2007) and pancreatic cancer (Park et al 2006). It has been suggested that future studies investigating chemoprotective roles of ginger constituents in human cancers should include human intervention trials (Shukla & Singh 2007).

Ginger and moxibustion — a clinical perspective

Moxibustion as a part of acupuncture has been well noted in TCM and is widely accepted as a useful complementary and alternative medicine therapy (Okada & Kawakita 2009). Indirect moxibustion utilises ginger slices placed at specific acupuncture points to insulate the skin from burning moxa sticks and provides therapeutic effects via thermal stimulation and sympathetic vibration (Shen et al 2006).

A review of 587 acupuncture and moxibustion randomised controlled papers from 1978 to 2007 conducted by Du et al 2009 demonstrated the growing indications for, and applications of, the use of moxibustion and acupuncture. Clinical trials have shown ginger partitioned moxibustion to be therapeutically effective in the treatment of child diarrhoea (Liu et al 2003), cervical vertigo (Xiaoxiang 2006), poststroke urination disorders (Liu & Wang 2006), leukopenia induced by chemotherapy (Zhao et al 2007) and rheumatoid arthritis (Xie & Lei 2008).

OTHER ACTIONS

Antihistamine

Shogaols and certain gingerols exhibit dose-dependent inhibition of drug-induced histamine release from rat peritoneal mast cells in vitro (Yamahara et al 1995).

Anxiolytic

A combination of ginger and *Ginkgo biloba* has been shown to reduce anxiety in an animal model (elevated plus-maze test). The effect was similar to

diazepam (Hasenohrl et al 1996). A highly non-polar fraction of a ginger extract has been shown to possess anticonvulsant, anxiolytic and antiemetic activities in animals (Vishwakarma et al 2002).

Antifibrotic

Supplementation with 5 g ginger not only prevented a decrease, but also significantly increased fibrinolytic activity in 30 healthy adult volunteers who consumed 50 g fat in a meal in an open clinical study (Verma & Bordia 2001).

Positive inotrope

Gingerols and shogaols isolated from ginger have positive inotropic activity, as demonstrated on isolated heart muscle (Shoji et al 1982, Yamahara et al 1995). The effect of gingerol seems to be rather specific to SR Ca^{2+}–ATPase activity (Kobayashi et al 1987).

Thermogenic

Ginger helps to maintain body temperature and inhibit serotonin-induced hypothermia in vivo (Huang et al 1991, Kano et al 1991). However, the addition of a ginger-based sauce to a meal did not produce any significant effect on metabolic rate in humans (Henry & Piggott 1987).

Hypotensive

Aqueous ginger extract has been shown to lower blood pressure via stimulation of muscarinic receptors and blockade of Ca^{2+} channels in guinea pig atria (Ghayur et al 2005). The calcium channel blocking effect of ginger has been demonstrated in acetycholine (ACh) induced airway constriction of mouse lung tissue. Pretreatment with a 70% aqueous methanolic crude extract of ginger 30 min prior to ACh administration achieved significant reduction in airway contraction and Ca^{2+}. Similar results were achieved with verapamil, indicating comparable modes of action. Concomitant use of both ginger extract and verapamil achieved the same outcome as when each was used alone (Ghayur et al 2008).

CLINICAL USE

Although ginger is used in many forms, including fresh ginger used in cooking or chai (Indian spicy tea), pickled or glazed ginger, ethanol extracts and concentrated powdered extracts, preparations made with the root are used medicinally. Depending on the specific solvent used, the resultant preparation will contain different concentrations of the active constituents and may differ markedly from crude ginger. Although the great majority of research refer specifically to the species *Zingiber officinale*, there is the potential for confusion with other species or even with other genera (Canter 2004). Furthermore, there are reported to be wide variations in the quality of commercial ginger supplements with concentrations of gingerols ranging from 0.0 to 9.43 mg/g. As such, the results of specific extracts cannot necessarily be extrapolated to different preparations (Schwertner et al 2006).

Prevention of nausea and vomiting

Many clinical studies have investigated the effects of ginger in the prevention and treatment of nausea and vomiting associated with different circumstances, including pregnancy (Fischer-Rasmussen et al 1990, Keating & Chez 2002, Portnoi et al 2003, Smith et al 2004, Sripramote & Lekhyananda 2003, Vutyavanich et al 2001, Willetts et al 2003), the postoperative period (Arfeen et al 1995, Bone et al 1990, Meyer et al 1995, Phillips et al 1993, Visalyaputra et al 1998), motion sickness (Grontved & Hentzer 1986, Lien et al 2003, Mowrey & Clayson 1982, Schmid et al 1994, Stewart et al 1991) and chemotherapy (Manusirivithaya et al 2004, Meyer et al 1995, Sontakke et al 2003).

A systematic review of 24 randomised controlled trials (RCTs) covering 1073 patients suggests that results for the treatment of nausea and vomiting in pregnancy are encouraging and generally supportive; however, results for postoperative nausea and vomiting and motion sickness are unclear and daily doses of up to 6 g of ginger seem to have few side effects (Betz et al 2005). More reviews provide further encouragement and suggest that ginger may indeed be effective in nausea associated with pregnancy (Boone & Shields 2005) and the postoperative period (Chaiyakunapruk et al 2006). Similarly a review of four well-controlled, double-blind, randomised clinical studies concluded there was convincing evidence for application of ginger in the treatment of nausea and vomiting of pregnancy (Bryer 2005).

Nausea and vomiting in pregnancy

There is supportive evidence from clinical studies that ginger preparations in pregnancy reduce the duration and severity of nausea and vomiting.

Nausea of pregnancy

There are many studies, including an observational study (Portnoi et al 2003) and at least six RCTs (Fischer-Rasmussen et al 1990, Keating & Chez 2002, Portnoi et al 2003, Smith et al 2004, Sripramote & Lekhyananda 2003, Vutyavanich et al 2001, Willetts et al 2003), as well as multiple systematic reviews, including a Cochrane review, that suggest that ginger powder or extract may be safe and effective in treating nausea and vomiting of pregnancy (Boone & Shields 2005, Borrelli et al 2005, Bryer 2005, Dib & El-Saddik 2004, Ernst & Pittler 2000, Jewell 2003). A subsequent review, considering six

> ***Clinical note — Morning sickness***
>
> Nausea and vomiting are the most common symptoms experienced in early pregnancy, with nausea affecting between 70% and 85% of women. About half of pregnant women experience vomiting (Jewell & Young 2002). Hyperemesis gravidarum is more severe and affects between 0.3% and 2% of all pregnant women. It is a multifactorial disease in which pregnancy-induced hormonal changes associated with concurrent gastrointestinal dysmotility and possible *Helicobacter pylori* infection function as contributing factors (Eliakim et al 2000).

double-blind RCTs with a total of 675 participants, and a prospective observational cohort study of 187 women, suggest that ginger is superior to placebo and as effective as vitamin B_6 in relieving pregnancy-related nausea and vomiting and that there is an absence of significant side effects and adverse pregnancy outcomes (Borrelli et al 2005).

In three double-blind, placebo-controlled, randomised trials of ginger for pregnancy-related nausea and vomiting, including one trial on hyperemesis gravidarum, 1 g ginger in divided doses was significantly more effective than placebo in reducing nausea and vomiting (Fischer-Rasmussen et al 1990, Keating & Chez 2002, Vutyavanich et al 2001). In a further double-blind trial of 120 women, 25 mg of the ginger extract EV.EXT 35 (equivalent to 1.5 g of dried ginger) four times daily was useful in patients experiencing nausea and retching, although no significant result was seen for vomiting (Willetts et al 2003).

Comparative studies

More recently, a comparative double-blind randomised controlled trial of 170 pregnant women who attended an antenatal clinic with the symptoms of nausea and vomiting in pregnancy found one capsule of ginger (0.5 g ginger powder) twice daily was identical in efficacy to treatment with 50 mg dimenhydrinate twice daily. In addition, ginger treatment resulted in fewer side effects (Pongrojpaw et al 2007). Initial comparative randomised, double-blind controlled trials found ginger to be equivalent to vitamin B_6 in helping to reduce pregnancy-related nausea, dry retching and vomiting (Smith et al 2004, Sripramote & Lekhyananda 2003). However, ginger (650 mg qid) proved more effective than vitamin B_6 (25 mg qid) in a randomised double-blind controlled trial involving 126 pregnant women, with a gestational age of ≤ 16 weeks who had nausea and vomiting (Chittumma et al 2007). Investigations over a 3-month duration into the efficacy of ginger compared to vitamin B_6 of 70 pregnant women with nausea, a gestational age of ≤ 17 weeks were randomised to receive either ginger 1 g/day or vitamin B_6 40 mg/day for 4 days. Treatment with ginger was found to be more effective than vitamin B_6 for relieving the severity of nausea, as well as equally effective in decreasing the episodes of vomiting (Ensiyeh & Sakineh 2008).

Postoperative nausea

Ginger may be useful for the prevention of postoperative nausea; however, not all studies have produced positive results and as the ginger preparations used have not been standardised, it is difficult to directly compare studies. A recent meta-analysis of five randomised trials, however, including a total of 363 patients found that a fixed dose of at least 1 g of ginger was more effective than placebo for the prevention of postoperative nausea and vomiting (Chaiyakunapruk et al 2006).

Most of the studies on postoperative nausea and vomiting have been done on patients undergoing gynaecological surgery. In two such randomised, placebo-controlled, double-blind studies, ginger significantly reduced the incidence of postoperative nausea and vomiting (Bone et al 1990, Phillips et al 1993), although two further studies failed to show any benefit with ginger (Arfeen et al 1995, Eberhart et al 2003). A fifth study of 80 women undergoing gynaecological laparoscopy found that 1 g of ginger taken 1 hour before surgery was significantly superior to placebo in reducing the incidence of nausea 2–4 hours afterwards; however, it failed to show statistical significance for an observed reduction in the incidence and frequency of vomiting (Pongrojpaw & Chiamchanya 2003).

A double-blind randomised controlled trial of 120 patients who underwent major gynaecological surgery found that a pretreatment with ginger powder (0.5 g) as compared to placebo resulted in lower incidence and frequency of vomiting in the treatment group. Frequency of vomiting was evaluated at 0, 2, 6, 12, and 24 hours postoperatively with the most statistically significant differences between ginger and placebo occurring at the 2- and 6-hour time intervals (Nanthakomon & Pongrojpaw 2006). Similarly a randomised study of 60 inpatients who underwent laparoscopic operations for non-cancer gynaecological conditions found that pretreatment 1 hour prior to surgery with three capsules of ginger (0.5 g of ginger powder per capsule) when compared to placebo significantly prevented vomiting at 6 hours postoperation. The effect was not apparent at 2 hours postoperation (Apariman et al 2006).

Although other types of surgery have not been as extensively studied as gynaecological surgery, there is a report on 6 months of clinical anaesthetic experience that suggests that a nasocutaneously administered 5% solution of essential oil of ginger given pre-operatively, together with conventional therapies, to general anaesthesia patients at high risk for postoperative nausea and vomiting is a safe and cost-effective way of reducing nausea and vomiting post anaesthesia (Geiger 2005).

In the only double-blind, placebo-controlled study of postoperative nausea and vomiting in patients undergoing middle ear surgery, ginger was ineffective and the use of 1 g of ginger 1 hour before surgery was associated with significantly more postoperative nausea and vomiting than the use of ondansetron or placebo (Gulhas et al 2003).

Motion sickness

Commission E approves the use of ginger root for the prevention of motion sickness (Blumenthal et al 2000) and several clinical studies have assessed its effects as either prophylaxis or treatment. An early double-blind, randomised, placebo-controlled study involving 80 naval cadets found that ginger was significantly superior to placebo in reducing symptoms of vomiting and cold sweats due to seasickness. Fewer symptoms of nausea and vertigo were also reported with ginger, but the difference was not statistically significant (Grontved & Hentzer 1986). In another randomised double-blind study of seasickness involving over 1700 tourists on a whale-watching safari 300 km north of the Arctic circle, 500 mg ginger was found to be as effective for the treatment of motion sickness as several

common antiemetic medications (cinnarizine, cyclizine, dimenhydrinate, domperidone, meclizine and scopolamine) with ginger preventing seasickness in 80% of the subjects during the 6-hour boat trip, although the incidence of severe vomiting did not differ significantly between treatment groups (Schmid et al 1994).

At least three studies have had mixed results from experimental models of motion sickness whereby subjects are seated in a rotating chair. The first study involving 28 volunteers found no significant protective effects for powdered ginger (500 mg or 1000 mg) or fresh ginger root (1000 mg) (Stewart et al 1991), whereas a second study involving 36 undergraduate men and women who reported very high susceptibility to motion sickness found that ginger was superior to dimenhydrinate (Mowrey & Clayson 1982). Another double-blind, randomised, placebo-controlled crossover study showed positive benefits with ginger pretreatment on prolonging time before nausea, shortening recovery time and effectively reducing nausea (Lien et al 2003). This study used pretreatment doses of 1000 mg and 2000 mg, which were also shown to reduce tachygastria and plasma vasopressin.

Chemotherapy-induced nausea

In an open study, 1.5 g ginger was found to decrease psoralen-induced nausea in 11 patients treated with photopheresis for cutaneous T-cell lymphoma (Meyer et al 1995).

Powdered ginger root effectively reduced cyclophosphamide-induced nausea and vomiting in a randomised, prospective, crossover double-blind study, with the antiemetic effect of ginger being equal to metoclopramide (Sontakke et al 2003). Ginger was found to have similar efficacy to metoclopramide in reducing cisplatin-induced emesis in a randomised, double-blinded, crossover study of 48 gynaecological cancer patients receiving chemotherapy (Manusirivithaya et al 2004). In a study of 28 cancer patients receiving chemotherapy for the first time, patients receiving high protein meals with ginger for 3 days beginning the day after chemotherapy were found to experience a reduction in delayed nausea and a reduced need for antiemetic medications compared to control groups (Levine et al 2008). However, a randomised, double-blind, placebo-controlled trial in 162 patients with cancer receiving chemotherapy and a previous experience of chemotherapy-induced nausea and vomiting found ginger (either 1 g or 2 g daily) provided no additional benefits for nausea prevention when given with 5-HT(3) receptor antagonists and/or aprepitant (Zick et al 2009).

Musculoskeletal disorders

Ginger is described in Ayurvedic (traditional Indian) and Tibb (traditional Arabian) systems of medicine to be useful in inflammation and rheumatism and this traditional use is supported by modern studies demonstrating ginger's anti-inflammatory activity.

A randomised, double-blind, placebo-controlled, multicentre, parallel-group 6-week study of 261 patients found that a highly purified and standardised ginger extract (EV.EXT 77) moderately reduced the symptoms of osteoarthritis (OA) of the knee (Altman & Marcussen 2001). Similarly, 250 mg of the ginger extract (Zintona EC) four times daily for 6 months was shown to be significantly more effective than placebo in reducing pain and disability in 29 OA patients in a double-blind, placebo-controlled, crossover study (Wigler et al 2003).

These studies are supported by an open retrospective study involving 56 patients (28 with RA, 18 with OA, 10 with muscular discomfort) that revealed that more than three quarters experienced varying degrees of relief of pain and swelling from the long-term use of powdered ginger (Srivastava & Mustafa 1992). Further support comes from studies comparing ginger to NSAIDs.

In one double-blind, randomised, placebo-controlled trial involving 120 patients, 30 mg of an ethanolic ginger extract equivalent to 1 g of ginger and prepared from fresh ginger purchased from a local market in India was found to be significantly more effective than placebo and was as effective as 1.2 g of ibuprofen in the symptomatic treatment of OA (Haghighi et al 2005). In another double-blind crossover study, 170 mg of the ginger extract EV.EXT 33 with a standardised content of hydroxy-methoxy-phenyl compounds given twice daily was found to be significantly more effective than placebo but not as effective as ibuprofen in reducing pain and disability in 75 patients with OA before the crossover period, whereas no statistical difference was seen between ginger and placebo in the analysis after the crossover period. The authors commented that the washout period may have been insufficient and that ginger might need to be administered for longer than 3 weeks, and possibly in a higher dosage, to be clinically effective (Bliddal et al 2000).

Dysmenorrhoea

Ginger has been used orally to treat dysmenorrhoea. Due to its ability to inhibit thromboxane synthetase and activate endorphin receptors, the use of ginger has been suggested in treatment of dysmenorrhoea (Backon 1991). A double-blind comparative clinical trial involving 150 participants demonstrated that ginger (250 mg ginger rhizome powder qid for 3 days from the start of their menstrual period) was just as effective as 250 mg mefenamic acid or 400 mg ibuprofen capsules in relieving pain in women with primary dysmenorrhoea (Ozgoli et al 2009).

Dyspepsia

Ginger stimulates the flow of saliva, bile and gastric secretions and therefore is traditionally used to stimulate appetite, reduce flatulence and colic, gastrointestinal spasms and generally act as a digestive aid. Commission E approves the use of ginger root for the treatment of dyspepsia (Blumenthal et al 2000).

Hyperlipidaemia

A double-blind controlled clinical trial of 85 volunteers with hyperlipidaemia showed ginger treatment (3 g/day) produced a significant lipid lowering

effect compared to controls. Measurement of lipid concentrations before and after 45 days of treatment showed significantly higher mean changes in triglyceride and cholesterol levels for ginger compared to control ($P < 0.05$) as well as significant mean reduction in LDL level and increase in HDL levels compared to controls (Alizadeh-Navaei et al 2008). This initial study shows promising results, however further controlled human trials are necessary to prove efficacy.

Migraine

Ginger is used to prevent and treat migraine headache. Its ability to inhibit thromboxane A2 and exert antihistamine, anti-inflammatory and gastric actions makes it a theoretically attractive choice (Mustafa & Srivastava 1990). This use is supported by an open-label study of 30 migraine sufferers that reported that treatment with a sublingual ginger and feverfew preparation (GelStat MigraineO) in the initial phase of a migraine resulted in most patients being satisfied with the therapy and being pain-free or only having mild headache post-treatment (Cady et al 2005).

OTHER USES

Ginger cream or compress is used externally for mastitis.

Diabetes

Ginger may also have potential benefits in the treatment of diabetes according to some promising animal studies indicating that ginger improves insulin sensitivity and reduces serum glucose levels. Clinical trials are required to confirm the significance of these findings in humans.

Weight loss

Further investigations in animal models suggest a potential role for ginger in weight loss. A significant reduction in body weight and parmetrial adipose tissue following oral administration of zingerone in ovariectomised rats indicated that by increasing norepinephrine-induced lipolysis in adipocytes, zingerone may prevent fat storage (Han et al 2008). The anti-obesity action of ginger may be a result of slowed intestinal absorption of dietary fat (Han et al 2005).

Asthma

A possible therapeutic role for gingerol in the treatment of asthma has been indicated through a recent animal model. An aqueous ginger extract enriched in *n*-gingerols was investigated in Th2-mediated pulmonary inflammation where gingerols were found to decrease recruitment of eosinophils to the lungs and suppress Th2 cell response to allergen. Serum IL-4, IL-5 and IgE titres were diminished in ginger-treated mice relative to controls (Ahui et al 2008).

Ulcerative colitis

Recent research has identified a potential role for ginger in attenuating inflammatory bowel disease. In an in vitro study involving ulcerated male wistar rats, ginger extract was found to be comparable to sulfasalazine in attenuating colonic mucosal injury. The effect of ginger against acetic acid-induced ulcerative colitis has been attributed to its anti-inflammatory and antioxidant properties (El-Abhar et al 2008). Clinical trials are required to determine the significance of this effect in humans.

DOSAGE RANGE

The recommended dose ranges widely from 500 mg to 9 g/day dried root or equivalent; however, a safe maximal dose is 4 g/day. As there are wide variations in the gingerol concentrations in commercial ginger supplements (Schwertner et al 2006), the effective dosage will depend on the preparation and the indication for use.

- Liquid extract (1:2): 0.7–4.0 mL/day.
- Dried root: 1–3 g daily in divided doses.
- Infusion: 4–6 slices of fresh ginger steeped in boiling water for 30 minutes.

According to clinical studies

- Dysmenorrhoea: 250 mg ginger rhizome powder taken four times daily for 3 days from the start of the menstrual period.
- Hyperlipidaemia: 3 g/day.
- Nausea and vomiting of pregnancy: 1–2 g taken daily in divided doses.
- Motion sickness: powdered ginger (500 mg or 1000 mg) or fresh ginger root (1000 mg) up to 2000 mg.
- Osteoarthritis: 250 mg of the ginger extract (Zintona EC) four times daily.
- Prevention of postoperative nausea: 1 g 1 hour prior to surgery.
- Rheumatoid arthritis: 1–2 g/day of powdered ginger.

ADVERSE REACTIONS

Gastric irritation, heartburn and bloating have been reported in clinical trials (Arfeen et al 1995). Contact dermatitis of the fingertips has also been reported (Seetharam & Pasricha 1987) with topical use.

SIGNIFICANT INTERACTIONS

Controlled studies are not available for many interactions; therefore they are based on evidence of activity and are largely theoretical and speculative.

Warfarin

Due to the herb's antiplatelet effects there is a theoretical risk of increased bleeding at high doses (> 10 g) although this is not evident clinically. There is no evidence of an interaction with warfarin at the usual dietary and therapeutic intakes (Jiang et al 2005, Stenton et al 2001, Vaes & Chyka 2000), and ginger has been shown not to alter prothrombin times in pooled human plasma collected from male volunteers between the ages of 18 and 57 years (Jones et al 2001). A standardised ginger extract, EV.EXT 33, has demonstrated no significant effect on coagulation parameters or on warfarin-induced changes in blood coagulation in rats (Weidner & Sigwart 2000) and ginger was found not to affect clotting status or the pharmacokinetics or pharmacodynamics of warfarin in healthy human subjects (Jiang et al 2005).

A study of 24 subjects found that ginger did not significantly affect clotting status or pharmacokinetics of warfarin in healthy subjects (Jiang et al 2006).

Due to the potential seriousness of the proposed interaction, people taking warfarin should use high-dose supplements (> 10 g/day) with caution.

Antiplatelet drugs

Theoretically, increased antiplatelet and anti-inflammatory effects may occur with high-dose ginger preparations, but the clinical significance of this is unknown. Caution should be exercised with doses > 10 g — possible beneficial effect.

Cisplatin

Pretreatment has restored testicular antioxidant parameters and sperm motility in cisplatin-induced damage in an animal model (Amin & Hamza 2006). Clinical implications are uncertain; however, potential benefits may be found upon further testing.

CONTRAINDICATIONS AND PRECAUTIONS

Ginger in high doses is not recommended for children under 6 years of age due to the pungent nature of ginger. However, if the benefits of ginger treatment outweigh the potential for gastric irritation, then it can be used. Alternatively, ginger lollies or ginger ale is sometimes used and a dose of 250 mg every 4 hours for motion sickness is safe.

Commission E suggests that people with gallstones consult with their physician before using ginger. People with gastric ulcers or reflux should use this herb with caution. Suspend use of high-dose supplements (> 10 g) 1 week before major surgery.

PREGNANCY USE

Although Commission E suggests that ginger is contraindicated in pregnancy, more recent research suggests that ginger is not contraindicated in pregnancy — doses up to 2 g/day of dried ginger root have been used safely.

No adverse effects on pregnancy were observed in multiple studies of ginger for nausea and vomiting (Boone & Shields 2005, Borrelli et al 2005, Bryer 2005, Dib & El-Saddik 2004, Ernst & Pittler 2000, Jewell 2002).

PRACTICE POINTS/PATIENT COUNSELLING

- Ginger is most often used for its antiemetic, anti-inflammatory and gastrointestinal effects.
- There is good clinical support for the use of ginger in the treatment of nausea and vomiting associated with pregnancy and some evidence for its use in motion sickness, the postoperative period and chemotherapy although this is less consistent.
- Ginger is traditionally used for gastrointestinal disorders including dyspepsia, poor appetite, flatulence, colic, vomiting, diarrhoea and spasms, as well as a diaphoretic in the treatment of the common cold and influenza.
- Ginger is also used as an anti-inflammatory agent for arthritis, although large controlled studies have yet to produce strong support for this use.
- Although antiplatelet effects have been reported, these require very large doses and are not likely to be significant in normal therapeutic doses or dietary intake levels.

PATIENTS' FAQs

What will this herb do for me?

Ginger is a useful treatment for nausea and vomiting associated with pregnancy and may also be of benefit in motion sickness, postoperative nausea and seasickness. It is also useful for treating symptoms of dyspepsia and may have symptom-relieving effects in arthritis, although this is less certain.

When will it start to work?

In the case of dyspepsia and motion sickness prevention, ginger will have an almost immediate effect, with improvement reported within 30 minutes. For motion sickness, 0.5–1.0 g ginger should be taken 30 minutes before travel and repeated 4 hourly. For nausea of pregnancy it should be taken for at least 4 days; however, symptoms should start to reduce within 1 hour of administration.

Are there any safety issues?

Ginger is well tolerated, although it should be used with caution by people with gallstones, gastric ulcers or reflux.

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Ginkgo biloba

HISTORICAL NOTE *Ginkgo biloba* is one of the world's oldest living tree species, earning it the name 'living fossil'. Its existence can be traced back more than 200 million years and it was commonly found in North America and Europe before the Ice Age. Its place of origin is believed to be remote mountainous valleys of Zhejiang province of eastern China and up to 350 years ago, knowledge about this plant was restricted to China (Singh et al 2008). Ginkgo was first introduced into Europe in 1690 by the botanist Engelbert Kaempfer, who described it as the 'tree with duck feet'. Ginkgo has been used medicinally for decades and is now one of the most popular therapeutic agents prescribed in Europe by medical doctors. It has been estimated that in Germany and France, prescriptions for ginkgo make up 1% and 1.3%, respectively, of total prescription sales (Pizzorno & Murray 2006). Also popular in the United States, it was the top-selling herbal medicine in 1999 with sales of US$148 million.

Current estimates indicate that the use of *G. biloba* has been growing at a very rapid rate worldwide at 25% per year in the open world commercial market (Singh et al 2008). Germany, Switzerland and France have respectively 31%, 8% and 5% of the world commercial market. To meet the demand for ginkgo products, 50 million *G. biloba* trees are grown, especially in China, France and South Carolina, USA, producing 8000 tons of dried leaves each year.

COMMON NAME

Ginkgo

In England, it is known as 'Maidenhair tree' based on its resemblance to the foliage of the 'Maidenhair fern' (*Adiantum*). In Japan, it is known as 'Ginkyo' and in France, 'L'arbre aux Quarante ecus' and 'Noyer Du Japon' (Singh et al 2008).

OTHER NAMES

Adiantifolia, *Arbre aux quarante ecus*, bai guo ye, duck foot tree, fossil tree, gin-nan, icho, Japanese silver apricot, kew tree, maidenhair tree, salisburia, silver apricot, tempeltrae, temple balm, yinhsing

BOTANICAL NAME/FAMILY

Ginkgo biloba (family Ginkgoaceae)

PLANT PARTS USED

In modern times only the leaf is used, but traditionally the nut was also used.

CHEMICAL COMPONENTS

Important constituents present in the leaves are the terpene trilactones (i.e. ginkgolides A, B, C and J and bilobalide), many flavonol glycosides, biflavones, proanthocyanidins, alkylphenols, simple phenolic acids, 6-hydroxykynurenic acid, 4-O-methylpyridoxine and polyprenols (van Beek 2002). *G. biloba* contains more than 30 genuine flavonoids, of which the flavonol glycosides are the most abundant (Singh et al 2008).

There has been some interest in ginkgo alkylphenols (ginkgolic acids) because of their allergenic

Clinical note — Ginkgo extract used in practice
The standardised ginkgo extract is made from dried ginkgo leaves extracted in 60% acetone. Only a fraction of the leaf matter is extracted, 98% is not extracted. Of the 2% extracted, the flavones account for 25%, the ginkgolides 3% and the bilobalide 3%. The remaining 69% is not specified. The drug ratio may vary from 35:1 to 67:1 (average ratio 50:1). This means that, on average, it takes 50 kg dried leaf to produce 1 kg of extract. Standardised ginkgo extract (e.g. EGb 761) must be standardised to 22–27% flavone glycosides, 5–7% terpenes lactones (2.8–3.4% ginkgolides A, B and C, and 2.6–3.2% bilobalide). The content of ginkgolic acids must be less than 5 ppm (Blumenthal et al 2000). Although the standardisation is very specific, the compounds are considered to be marker compounds, as the active constituents of *G. biloba* have not been fully identified (unpubl. data: Keller K, Chair of the Herbal Medicinal Products Working Group, European Medicines Evaluation Agency. Quality Assurance of Herbal Medicines, March 2001).

properties, so most manufacturers limit the concentration of alkylphenols to 5 ppm.

MAIN ACTIONS

The many and varied pharmacological actions of ginkgo preparations are related to the presence of several classes of active constituents.

Antioxidant

G. biloba extract and several of its individual constituents, such as quercetin and kaempferol, have demonstrated significant antioxidant properties in vitro (Hibatallah et al 1999, Sloley et al 2000). Antioxidant activity has further been demonstrated in several different animal models.

Experimental models investigating the effects of ginkgo on reducing ischaemic injury have shown positive results, indicating that ginkgo reduces the damage caused by oxidative stress during reperfusion. One study using a model of myocardial infarction found that pretreatment with *G. biloba* extract EGb 761 reduced ischaemic myocardial injury compared to the untreated animals (Schneider et al 2008). Another in vivo study investigated the effects of *G. biloba* extract (EGb 761) on lung injury induced by intestinal ischaemia/reperfusion (II/R) (Liu et al 2007). The treated group received EGb 761 (100 mg/kg/day) via gastric tube for seven consecutive days prior to surgery, whereas the inactive group just received vehicle. Active treatment produced a significant protective effect on lung injury induced by II/R, which may be related to its antioxidant property and suppression of neutrophil accumulation and nitric oxide synthase (iNOS)-induced NO generation.

A novel study has investigated the effect of *G. biloba* on mobile phone-induced oxidative damage in brain tissue of rats (Ilhan et al 2004). Rats were exposed to the same amount of mobile phone-induced radiation for 7 days with some also pretreated with *G. biloba*. After exposure, oxidative damage was evident by the: (i) increase in malondialdehyde (MDA) and nitric oxide (NO) levels in brain tissue, (ii) decrease in brain superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) activities and (iii) increase in brain xanthine oxidase (XO) and adenosine deaminase (ADA) activities. *Gingko biloba* prevented these alterations and the mobile phone-induced cellular injury in brain tissue histopathologically.

Topical antioxidant effects have also been investigated. *G. biloba* has been shown to reduce the effects of UV radiation on skin (Aricioglu et al 2001, Hibatallah et al 1999, Kim 2001, Lin & Chang 1997). When applied topically, ginkgo increases the activity of SOD within skin, thereby enhancing the skin's natural defences.

Vascular effects

Vasodilation

Ginkgo promotes vasodilation and improves blood flow through arteries, veins and capillaries. Increases in microcirculatory blood flow occur rapidly and have been confirmed under randomised crossover test conditions 1 hour after administration (Jung et al 1990).

Several mechanisms of action are responsible. Currently, these are considered to be: inhibition of NO release, activation of Ca^{2+}-activated K^+ (K_{Ca}) channels, and increased prostacyclin release (Chen et al 1997, Koltermann et al 2007, Nishida & Satoh 2003). In 2008, a clinical study was published which provides further information about the mechanisms involved. Wu et al investigated the effects of *G. biloba* extract (GBE) on the distal left anterior descending coronary artery (LAD) blood flow and plasma nitric oxide (NO) and endothelin-1 (ET-1) levels (Wu et al 2008). The randomised study of 80 volunteers with coronary artery disease (CAD) used Doppler echocardiography to determine blood flow, which was measured at baseline and after 2 weeks of treatment. A significant improvement in maximal diastolic peak velocity, maximal systolic peak velocity and diastolic time velocity integral was observed for the group treated with GBE compared with controls ($P < 0.01$). Additionally, a significant increase in NO and decrease in ET-1 was observed, suggesting that the observed increase of LAD blood flow might be related to restoration of the delicate equilibrium between NO and ET-1.

Reduces oedema

Various flavonoids, including anthocyanosides and *G. biloba* extracts, have been shown to be effective against experimentally induced capillary hyperfiltration (Cohen-Boulakia et al 2000).

Antiplatelet and anticoagulant

There have been several case reports of *G. biloba* causing haemorrhage during or after surgery (Hauser et al 2002, Schneider et al 2002) and there is evidence that one of its components, ginkgolide

B, is a platelet-activating factor antagonist (Smith et al 1996). One clinical study demonstrated that EGb 761 (80 mg/day) produced a significant reduction in blood viscosity after 30 days' treatment (Galduroz et al 2007). When measured again 90 days after commencement of EGb 761 treatment, a further reduction was observed which appeared to stabilise, as no further reduction was observed after 180 days of use.

In contrast, at least 10 clinical studies have found no evidence of significant bleeding or platelet effects due to *G. biloba* ingestion (Aruna & Naidu 2007, Bal Dit et al 2003, Beckert et al 2007, Carlson et al 2007, Engelsen et al 2003, Gardner et al 2007, Jiang et al 2005, Kohler et al 2004, Lovera et al 2007, Wolf 2006). Studies have included young healthy volunteers, older adults, people with multiple sclerosis and people using warfarin or aspirin at the same time as *G. biloba*. An escalating dose study found that 120 mg, 240 mg or 480 mg given daily for 14 days did not alter platelet function or coagulation (Bal Dit et al 2003).

Alters neurotransmitters

Monoamine oxidase (MAO) inhibition

In vitro tests in rat brains suggest that EGb 761 may exert MAO-A and MAO-B inhibitor activity (Wu & Zhu 1999). Tests with isolated constituents, kaempferol, apigenin and chrysin, have demonstrated these to be potent MAO inhibitors, with greater effect on MAO-A than MAO-B (Sloley et al 2000).

Alternatively, one human study using positron emission tomography (PET) found that treatment with *G. biloba* (EGb 761: 120 mg/day) for 1 month did not produce significant changes in brain MAO-A or MAO-B in the 10 participating volunteers (Fowler et al 2000).

Serotonin

Another in vitro study found that oral EGb 761 significantly increases the uptake of serotonin, but not dopamine, in cerebral cortex samples from mice (Ramassamy et al 1992). Another in vivo study identified an antiaggressive effect mediated by 5-HT_{2A} receptors (Shih et al 2000).

Cholinergic effects

Considering that *G. biloba* appears to be as effective as anticholinesterase drugs, several researchers have investigated whether it exerts cholinergic effects. Evidence from behavioural, in vitro and ex vivo tests with *G. biloba* has shown both direct and indirect cholinergic activities (Das et al 2002, Nathan 2000). The extract appears to increase the rate of acetylcholine turnover and stimulate the binding activity of ligands to muscarinic receptors in the hippocampus (Muller 1989).

Gamma aminobutyric acid (GABA) receptors

Bilobalide in *G. biloba* is a competitive antagonist for GABA-A receptors according to in vitro tests (Huang et al 2003). The effect is almost as potent as bicuculline and pictrotoxinin.

Corticosterone

In vivo tests have found that EGb 761 has stress-alleviating properties mediated through its moderation of corticosterone levels (Puebla-Perez et al 2003).

Neuroprotection

G. biloba leaf extract (EGb 761) has demonstrated neuroprotective effects in a variety of studies ranging from molecular and cellular, to animal and human; however, the cellular and molecular mechanisms remain unclear (Ao et al 2006, Smith et al 2002). Of the constituents studied, it appears that the bilobalide constituent is chiefly responsible for this activity, although others are also involved (DeFeudis & Drieu 2000).

Until recently, it was believed that the antioxidant, membrane-stabilising and platelet-activating factor antagonist effects were chiefly responsible for neuroprotection, but effects at the mitochondria may also be important contributing mechanisms.

Beta-amyloid

G. biloba extract EGb 761 protects cells against toxicity induced by beta-amyloid in a concentration-dependent manner, according to in vitro tests (Bastianetto & Quirion 2002a, 2002b; Bastianetto et al 2000). In vivo studies have confirmed that ginkgo extract has an antiamyloid aggregation effect (Luo 2006). It appears that ginkgo increases transthyretin RNA levels in mouse hippocampus, which is noteworthy because transthyretin is involved in the transport of beta-amyloid and may provide a mechanism to reduce amyloid deposition in brain (Watanabe et al 2001). There is also evidence that *G. biloba* modulates alpha-secretase, the enzyme that cuts the amyloid precursor protein and prevents amyloidogenic fragments from being produced (Colciaghi et al 2004).

Cerebral ischaemia

There is evidence from experimental and clinical studies that *G. biloba* extract protects tissues from ischaemia/reperfusion damage (Janssens et al 2000). According to investigation with an experimental model, EGb 761 could prevent and treat acute cerebral ischaemia, but the effect was most pronounced when administered prophylactically (Peng et al 2003).

Stabilisation and protection of mitochondrial function

Several in vitro tests have demonstrated that EGb 761 stabilises and protects mitochondrial function (Eckert et al 2005, Janssens et al 2000). These observations are gaining the attention of researchers interested in neurodegenerative diseases, as it is suspected that the mitochondria and the phenomenon of mitochondrial permeability transition play a key role in neuronal cell death and the development of such diseases (Beal 2003, Shevtsova et al 2005).

Immunostimulant

Immunostimulatory activity has been demonstrated in several experimental models (Puebla-Perez et al 2003, Tian et al 2003, Villasenor-Garcia et al 2004).

The beneficial effects of EGb 761 on immune function are based on its antioxidant properties, as well as the cell proliferation-stimulating effect.

Anti-inflammatory

The anti-inflammatory activity of ginkgo has been investigated for the whole extract and an isolated biflavonoid component known as ginkgetin, with both forms demonstrating significant anti-inflammatory activity.

Ginkgo extract

Intravenously administered ginkgo extract produced an anti-inflammatory effect that was as strong as the same dose of prednisolone (i.e. 1 mg GBE = 1 mg prednisolone) in an experimental model. Ginkgo extract was also found to significantly reduce the concentration of PGE_2, TNF-alpha and NO production in vitro (Ilieva et al 2004).

Studies with subcutaneously administered *G. biloba* extract in experimental models have also identified significant anti-inflammatory activity, with the addition of antinociceptive effects (Abdel-Salam et al 2004).

Investigation with an animal model of colitis revealed that *G. biloba* (EGb 761) extract reduces markers of inflammation (iNOS, COX-2 and TNF-alpha) and inflammatory stress (p53 and p53-phospho-serine 15) (Kotakadi et al 2008).

Ginkgetin

Ginkgetin showed a stronger anti-inflammatory activity than prednisolone when administered by intraperitoneal injection in an animal model of arthritis. Histological examination of the knee joints confirmed the effect (Kim et al 1999). When used topically in an animal model of chronic skin inflammation and pro-inflammatory gene expression, it was found to inhibit ear oedema by approximately 26% and PGE_2 production by 30% (Lim et al 2006). Histological comparisons revealed that ginkgetin reduced epidermal hyperplasia, inhibited phospholipase A2, and suppressed COX-2 and iNOS expression (Lim et al 2006).

Anticancer

Studies conducted with various molecular, cellular and whole animal models have revealed that leaf extracts of *G. biloba* may have anticancer (chemopreventive) properties that are related to its antioxidant, antiangiogenic and gene regulatory actions (DeFeudis et al 2003). Both the flavonoid and terpenoid constituents are thought to be responsible for many of these mechanisms, meaning that the whole extract is required for activity. Studies in humans have found that ginkgo extracts inhibit the formation of radiation-induced (chromosome-damaging) clastogenic factors and UV-induced oxidative stress, both effects that may contribute to the overall chemopreventive activity. As a result of these observations, there has been a call by some academics for ginkgo to be more widely investigated and used in the prevention and treatment of cancer (Eli & Fasciano 2006).

OTHER ACTIONS

Activity on cytochromes and P-glycoprotein

Several studies have investigated *G. biloba* for effects on different cytochromes in vitro and with various animal models. Four human studies have also been conducted. Early in vitro tests demonstrated that *G. biloba* inhibits CYP 3A4; however, clinical studies have found no such effect (Budzinski et al 2000, Gurley et al 2002, 2005, Markowitz et al 2003). In vitro tests have suggested that the effect on cytochromes is biphasic, with low doses of ginkgo extract inducing CYP 1A2 and inhibiting 2D6 and higher doses exhibiting the opposite effect (Hellum et al 2007). Studies investigating ginkgo extract and its various constituents in animal models have identified induction of CYP 3A1, 1A2, 2E1, 2B½ for ginkgo which appears to be largely mediated by the bilobalide constituent, whereas no effect on CYP 2D6, 2C11 or 2C7 has been demonstrated (Deng et al 2008, Tang et al 2007a, Zhao et al 2006).

The question arises of clinical significance and whether the effects observed in animal models also occur in humans to an appreciable degree. To this end, four clinical studies have been conducted clarifying the issue (Duche et al 1989, Gurley et al 2002, 2005, Markowitz et al 2003, Tang et al 2007a). Tests with human volunteers have found no significant effect on CYP 3A4, 2D6 or 1A2 with *G. biloba* extract.

Little is known about the effects of ginkgo on the drug transporter molecule P-glycoprotein (P-gp). Two in vitro studies have identified induction of P-gp with ginkgo; however, tests with human subjects are required to determine whether the effect occurs in vivo and its clinical significance (Hellum & Nilsen 2008, Yeung et al 2008).

CLINICAL USE

G. biloba is a complex herb that contains many different active constituents and works by means of multiple mechanisms. In practice, its therapeutic effect is a result of interactions between constituents and mechanisms, giving it applications in many varied conditions. To date, most of the research conducted in Europe has used a standardised preparation known as EGb 761, available commercially as Rokan, Tanakan or Tebonin.

Dementia, memory impairment

G. biloba has been used and studied as a cognitive activator in a variety of populations, such as cognitively intact people, those with cerebral insufficiency, age-related memory impairment, Alzheimer's dementia or multi-infarct dementia (Itil et al 1998, Le Bars et al 2000, 2002, Oken et al 1998, Wettstein 1999). It has also been tested in healthy adults with no cognitive deficits to determine whether treatment can further improve memory (Kennedy et al 2007b). Overall, the evidence suggests that oral ginkgo extract may improve cognitive function in people with mild-to-moderate cognitive impairment, but it is less successful in people with normal cognitive function. Long-term use does not appear to protect against the development of dementia.

A 2002 Cochrane review of the scientific literature concluded that *G. biloba* produces benefits superior to placebo within 12 weeks' treatment in people with acquired cognitive impairment, including dementia, of any degree of severity (Birks et al 2002). Cognition, activities of daily living and measures of mood and emotional function show significant benefit for ginkgo compared with placebo.

The most recent Cochrane review analysed results from 35 double-blind, placebo-controlled trials (n = 4247) which lasted from 3 weeks to 52 weeks, with the majority being of 12 weeks duration (Birks et al 2007). Subjects enrolled in the studies were diagnosed with dementia of any type or age-related cognitive impairment. Older studies (> 20 years ago) generally used sign and symptom questionnaires, whereas more recent studies used modern diagnostic criteria and computerised tomographic (CT) scans for dementia. All except one study used a standardised extract and the daily dose tested ranged from 80 to 600 mg/day but was mostly less than 200 mg/day.

The final meta-analysis used results from 29 studies that the reviewers described as heterogeneous, not allowing a consistent pattern of results to emerge. This may be in part due to reviewers pooling all studies regardless of patient diagnoses, the myriad of different scales and measures used and the fact that some studies are over 20 years old and randomisation and blinding techniques have changed in recent years. As a result, the findings are not straightforward and deserve more detailed description to be better understood.

Using the CGIC scale whereby clinical global improvement is assessed by the physician, ginkgo treatment produced benefits at doses greater than 200 mg/day at 24 weeks compared with placebo, but showed no effects at the lower doses. Benefits were defined as clinical improvement or no further deterioration. Studies that used the Sandoz Clinical Assessment-Geriatric (SCAG) scale, which assesses global function, also found that *G. biloba* produced benefits compared to placebo at low dose (< 200 mg/day) before and after 12 weeks of treatment. One study found a significant difference between treatment and control groups in Geriatric Evaluation by Relative's Rating Instrument (GERRI) scores but not in Clinical Global Impression of Change (CGIC).

Studies testing cognitive function showed that treatment for less than 12 weeks produced no significant effect; however, longer treatment produced a significant difference between *G. biloba* and placebo in favour of *G. biloba*, but the treatment effect is very variable. Activities of daily living showed benefit at 12 weeks (dose < 200 mg/day), but not at 24 weeks as assessed by different methods.

With regard to adverse effects, *G. biloba* was well tolerated with no significant differences compared with placebo. Whilst positive results emerged in the meta-analysis, reviewers concluded that the evidence indicating ginkgo has predictable and clinically significant benefit for people with dementia or cognitive impairment is inconsistent and unconvincing.

Clinical note — What is cerebral insufficiency?
Cerebral insufficiency is a syndrome characterised by a collection of symptoms, although it is not associated with any clear pathological changes. The 12 symptoms associated with this condition are: difficulties of memory and concentration, being absent-minded, confusion, lack of energy, tiredness, decreased physical performance, depressive mood, anxiety, dizziness, tinnitus and headaches (Kleijnen & Knipschild 1992). Some of these symptoms are also described as early symptoms of dementia and appear to be associated with decreased cerebral blood flow, although frequently no explanation is found.

In 2008, several more placebo-controlled studies were published. One randomised, double-blind, parallel-group trial of 176 subjects with mild-to-moderate dementia compared a standardised extract of *G. biloba* (120 mg daily) to placebo over 6 months (McCarney et al 2008). At this low dose, ginkgo did not provide benefits. A larger double-blind randomised study of 400 patients with dementia associated with neuropsychiatric features tested a higher dose of EGb 761 extract (240 mg/day) (Scripnikov et al 2007). The study population included people with probable or possible Alzheimer's disease (AD) with cerebrovascular disease or vascular dementia. EGb 761 was significantly superior to placebo with respect to the primary (Specialty Knowledge Test [SKT] battery) and all secondary outcome variables. Whilst herbal treatment improved outcomes, the placebo group showed evidence of deterioration as measured by the mean composite score (frequency × severity) and the mean caregiver distress score ($P < 0.001$). The largest effects for EGb 761 were found for apathy/indifference, anxiety, irritability/lability, depression/dysphoria and sleep/nighttime behaviour.

Another double-blind study of 400 subjects with mild-to-moderate dementia (AD or vascular dementia) with neuropsychiatric features tested EGb 761 extract over 22 weeks (Napryeyenko & Borzenko 2007). Active treatment produced a mean −3.2-point improvement in the SKT with an average deterioration by +1.3 points on placebo ($P < 0.001$). EGb 761 was significantly superior to placebo on all secondary outcome measures, including the Neuro Psychiatric Inventory (NPI) and an activities-of-daily-living scale. Treatment results were essentially similar for AD or vascular dementia subgroups. The drug was well tolerated; adverse events were similar for ginkgo and placebo treatment.

Use in healthy subjects

Many double-blind studies have investigated the effects of *G. biloba* (120–600 mg/day) on cognitive function in younger and older healthy subjects. Some studies have evaluated the effects of a single dose, whereas others are long-term studies (2 days–13 weeks).

The most recent systematic review of placebo-controlled trials was published in 2007 and investigated whether *G. biloba* enhances cognitive function

in healthy subjects aged under 60 years (Canter & Ernst 2007). A number of the acute studies included in the analysis used multiple outcomes and reported positive effects on one or more of these at particular time points with particular doses, but these findings were either not replicated, or contradicted by other studies. The evidence from long-term studies is largely negative. Of those studies that measured subjective effects, only one of five acute studies and one of six long-term studies reported any significant positive results.

Since this review, several new studies have been published. Overall, tests with younger subjects taking *G. biloba* long term have failed to show positive effects on memory; however, short-term benefits after acute dosing may be possible for some aspects of memory. Healthy older adults with poorer cognitive performance appear to experience greater benefit than those with higher cognitive function levels, according to the latest studies, but more research is required to confirm this initial observation.

Carlson et al conducted a 4-month, randomised, double-blind, placebo-controlled study of 90 men and women (age range 65–84 years) (Carlson et al 2007). Treatment consisted of placebo or a *G. biloba*-based supplement containing 160 mg *G. biloba*, 68 mg gotu kola and 180 mg docosahexaenoic acid per day for 4 months. Of the group, 78 subjects completed the study that found no significant differences in quality of life or adverse events. Researchers commented that high baseline scores for cognitive function may have contributed to the null findings.

Tests with younger (18–43 years) and older volunteers (55–79 years) produced different results in a 12-week, double-blind, placebo-controlled study (Burns et al 2006). The effects of ginkgo (120 mg/day) were assessed for both groups on a wide range of cognitive abilities, executive function, attention and mood. The older group responded to treatment as long-term memory assessed by associational learning tasks showed significant improvement with ginkgo; however, no other significant differences were found on any other measure. The young adult group ($n = 104$) failed to respond on any measure, as no significant differences were observed for the treatment or placebo groups. Similarly, no significant effects on mood or any of the cognitive tests employed by Elsabagh et al were found for ginkgo (120 mg/day) taken over 6 weeks in a placebo-controlled study of 52 young adults (Elsabagh et al 2005a). In contrast, acute treatment of younger subjects with ginkgo (120 mg) significantly improved performance on the sustained-attention task and pattern-recognition memory task according to a randomised, double-blind study (Elsabagh et al 2005a). The study of 52 students found no further effects for ginkgo on working memory, planning, mental flexibility or mood.

Kennedy et al reported on a re-analysis of data from three methodologically identical, double-blind, crossover studies that each included a treatment of 120 mg ginkgo extract and matched placebo (Kennedy et al 2007b). The analysis found that 120 mg of ginkgo conferred a significant improvement on the 'quality of memory' factor and was most evident at 1 and 4 hours after single-dose treatment, but had a negative effect on performance on the 'speed of attention' factor, which was most evident at 1 and 6 hours after treatment.

Ginkgo complexed with phospholipids

Some recent data suggest that the complexation of standardised GBE with soy-derived phospholipids may enhance the bioavailability of active components, thereby producing better results. Kennedy et al tested two different ginkgo products complexed with either phosphatidylserine or phosphatidylcholine in a placebo-controlled study of younger volunteers (Kennedy et al 2007a). Test subjects were given an acute dose of ginkgo, one of the ginkgo combinations or placebo on separate days (7 days apart). Confirming earlier results, *G. biloba* (120 mg) as sole treatment was not associated with markedly improved performance on the primary outcomes in this younger population; however, administration of GBE complexed with phosphatidylserine resulted in improved secondary memory performance and significantly increased speed of memory task performance across all of the postdose testing sessions. Interestingly, all three herbal treatments were associated with improved calmness. Whether the superior effect obtained for this combination is due to the complexation of the extracts, their mere combination or the separate psychopharmacological actions of the two extracts remains to be tested.

Cognitive effects in postmenopausal women

One week of treatment with ginkgo (120 mg/day) significantly improved attention, memory and mental flexibility in postmenopausal women according to a double-blind, placebo-controlled study (Elsabagh et al 2005b). The study tested ginkgo (LI 1370, Lichtwer Pharma, Marlow, UK) over 6 weeks, which significantly improved mental flexibility in women who began the trial with poorer cognitive performance (Elsabagh et al 2005b). Younger subjects with better cognitive performance at baseline did not experience any significant effects compared to placebo.

Comparisons with anticholinesterase drugs

The type of CNS effects produced by EGb 761 in elderly dementia patients is similar to those induced in tacrine responders and those seen after the administration of other 'cognitive activators', according to a small randomised study involving 18 elderly people diagnosed with mild-to-moderate dementia (possible or probable AD) (Itil et al 1998). The results also demonstrated that 240 mg EGb produced typical cognitive activator ECG profiles (responders) in more subjects (8 of 18) than 40 mg tacrine (3 of 18 subjects). A later review concluded that ginkgo extract and second-generation cholinesterase inhibitors (donepezil, rivastigmine, metrifonate) should be considered equally effective in the treatment of mild-to-moderate Alzheimer's dementia (Wettstein 2000).

Commission E approves the use of standardised ginkgo extract in dementia syndromes, including

vascular, primary degenerative and mixed types (Blumenthal et al 2000).

Dementia prevention

The many mechanisms attributed to ginkgo make it an ideal candidate for the long-term prevention of many age-related diseases such as dementia. Two clinical trials were published in 2008, which investigated whether treatment with *G. biloba* could significantly reduce the incidence of dementia.

DeKosky et al compared the effectiveness of *G. biloba* to placebo in reducing the incidence of all-cause dementia and AD in elderly individuals with normal cognition and those with mild cognitive impairment (MCI) (DeKosky et al 2008). The large randomised, double-blind, placebo-controlled clinical trial involved 3069 community dwelling subjects aged 75 years or older with normal cognition (n = 2587) or MCI (n = 482). It was conducted at five academic medical centres in the United States between 2000 and 2008 with a median follow-up of 6.1 years. Treatment consisted of a twice-daily dose of 120-mg extract of *G. biloba* and was not shown to reduce either the overall incidence rate of dementia or AD incidence in elderly individuals. Treatment was well tolerated by this population, as the incidence of side effects was similar for both groups.

The same year, Dodge et al published the results of a double-blind study involving 118 cognitively intact older subjects (85 years or older) (Dodge et al 2008). In the intention-to-treat analysis, there was no reduced risk of progression to clinical dementia among the GBE group; however, in the secondary analysis, where medication adherence level was controlled, the GBE group had a significantly lower risk of progression and a smaller decline in memory scores. Importantly, more stroke and transient ischaemic attack (TIA) cases were observed among the GBE group, which require further investigation to confirm.

Currently, two large double-blind, placebo-controlled studies are underway testing whether *G. biloba* (120 mg twice daily) is effective in the prevention of dementia in normal elderly people and those with early cognitive decline (Williamson et al 2008). The complete results from these studies are not expected for another few years.

Acute ischaemic stroke

G. biloba extract is widely used in the treatment of acute ischaemic stroke in China. A Cochrane systematic review identified 14 trials, of which 10 (792 patients) were included (Zeng et al 2005). In those 10 trials, follow-up was performed at 14–35 days after stroke and in all studies, neurological outcome was assessed, but none of them reported on disability (activities of daily living function) or quality of life (QOL) and only three trials reported adverse events. Nine of the trials were considered to be of inferior quality. Overall results from the 10 studies found that *G. biloba* extract was associated with a significant increase in the number of improved patients. Of note, one placebo-controlled trial, assessed to be of good quality, failed to show an improvement of neurological deficit at the end of treatment. In view of the shortcomings of many trials and limited evidence, high-quality and large-scale randomised controlled trials are still required to determine its efficacy.

Depression

Although studies that have investigated the effects of *G. biloba* in cerebral insufficiency, a syndrome that is often characterised by depression, have shown positive results, no clinical studies are available that have investigated its use in clinical depression.

One randomised, double-blind, placebo-controlled study has investigated its effects in seasonal affective disorder (SAD). *G. biloba* extract PN246, in tablet form (Bio-Biloba), was tested in 27 patients with SAD over 10 weeks or until they developed symptoms, starting in a symptom-free phase about 1 month before symptoms were expected. In this trial, *G. biloba* failed to prevent the development of SAD (Lingaerde et al 1999).

Cieza et al (2003) tested EGb 761 (240 mg/day) on the subjective emotional wellbeing of healthy older subjects (50–65 years) in a randomised, double-blind study. Ginkgo treatment produced a statistically significant difference for the visual analogue scale (VAS) mental health and for QOL, as well as for the Subjective Intensity Score Mood in week 2 compared with placebo. At the end of the study, statistically significant improvement in the EGb 761 group was observed for the variables: depression, fatigue and anger.

Several recent studies investigating the effects of ginkgo on memory have also measured effects on mood. The double-blind studies found no significant effects for healthy older or younger volunteers (Burns et al 2006, Carlson et al 2007, Elsabagh et al 2005a). Whether ginkgo may have a mood enhancing effect in a population with diagnosed depression remains to be tested.

Generalised anxiety disorder (GAD)

EGb 761 has demonstrated stress-alleviating and anxiolytic-like activity in preclinical studies, and most recently in a randomised study of 107 patients with GAD (n = 82) or adjustment disorder with anxious mood (n = 25) (Woelk et al 2006). *G. biloba* was tested in two different doses (480 mg and 240 mg/day) against placebo over 4 weeks and found to be significantly superior with a dose-response trend being identified. Beneficial effects were observed after 4 days of treatment. Additionally, ginkgo treatment was safe and well tolerated.

Peripheral vascular diseases

Ginkgo has been used in the treatment of intermittent claudication, Raynaud's syndrome and chilblains (Mouren et al 1994, Pittler & Ernst 2000).

Intermittent claudication

In 2000, a meta-analysis of eight clinical trials found a significant difference in the increase in pain-free walking distance in favour of *G. biloba* over placebo in intermittent claudication (Pittler & Ernst 2000). An earlier randomised study measuring transcutaneous partial pressure of oxygen during exercise

Clinical note — Peripheral arterial disease
PAD is the chronic obstruction of the arteries supplying the lower extremities. The most frequent symptom is intermittent claudication, which results from poor oxygenation of the muscles of the lower extremities and is experienced typically as an aching pain, cramping or numbness in the calf, buttock, hip, thigh or arch of the foot. Symptoms are induced by walking or exercise and are relieved by rest. Presently, medical treatment revolves around lifestyle changes, such as increased exercise, and surgery as a final option.

showed that a dose of 320 mg/day EGb 761 taken for 4 weeks significantly decreased the amount of ischaemic area by 38%, compared with no change with placebo (Mouren et al 1994).

A more recent 2004 meta-analysis confirmed that ginkgo is more effective than placebo in intermittent claudication (Horsch & Walther 2004). Nine double-blind studies of EGb 761 for intermittent claudication were assessed in a total of 619 patients. A sensitivity analysis of a homogeneous sample in terms of design, treatment duration, inclusion and exclusion criteria and methods of measurement confirms these findings. Most studies have used a dose of 120 mg/day taken in divided doses, although one trial found that 240 mg/day gave better results. It should be recommended as long-term therapy and as an adjunct to exercise for the best results.

A year later, Pittler and Ernst conducted a systematic review of all complementary therapies which may be useful as a treatment for intermittent claudication and identified *G. biloba* as the only effective herbal medicine to show better results than placebo (Pittler & Ernst 2005).

Commission E approved the use of standardised ginkgo extract for intermittent claudication (Blumenthal et al 2000).

Two double-blind, placebo-controlled studies found no significant effects for *G. biloba* on maximal walking time in people with claudication (Gardner et al 2008, Wang et al 2007). One study compared the effects of an exercise program with and without the addition of ginkgo treatment in 22 subjects (Wang et al 2007). Ginkgo was administered for 24 weeks at a dose of 240 mg/day and no differences were seen between the exercise-only phase and the exercise and herbal treatment phase. The other placebo-controlled study used a higher dose of *G. biloba* (EGb 761; 300 mg/day), which was administered for 4 months (Gardner et al 2008). Active treatment resulted in a modest but insignificant increase in maximal treadmill walking time and flow-mediated vasodilation in older people with peripheral arterial disease (PAD). The study included 62 adults, aged 70 ± 8 years (mean ± SD).

Raynaud's syndrome

A standardised *G. biloba* extract (Seredrin) taken over a 10-week period significantly reduced the number of attacks per week (from 13.2 to 5.8) compared with placebo, according to a randomised study (Muir et al 2002).

Vertigo, tinnitus and sudden deafness

Ginkgo is used to treat these and other symptoms of vestibule-cochlear disorders.

In 1999, a systematic review of five RCTs testing standardised *G. biloba* extracts in people whose primary complaint was tinnitus concluded that treatment with *G. biloba* may result in significant improvements in tinnitus (Ernst & Stevinson 1999). Three years later, a review of eight controlled trials in tinnitus confirmed these findings, stating that ginkgo is significantly superior to placebo or reference drugs when used for periods of 1–3 months (Holstein 2001).

However, results of two double-blind studies conducted more recently have shifted the evidence against the use of *G. biloba* in tinnitus. The first was a large, double-blind, placebo-controlled study involving 1121 people aged between 18 and 70 years with tinnitus and 978 matched controls, which found that 12 weeks of treatment with ginkgo extract, LI 1370 (Lichtwer Pharma, Berlin, Germany), 50 mg, three times daily resulted in no significant differences when subjects assessed their tinnitus in terms of loudness and how troublesome it was (Drew & Davies 2001). A more recent double-blind, placebo-controlled, randomised study of 66 subjects with tinnitus failed to show benefits with active treatment using a dose of 120 mg extract daily over 12 weeks (Rejali et al 2004). The primary outcome measures used were the Tinnitus Handicap Inventory, The Glasgow Health Status Inventory and the average hearing threshold at 0.5, 1, 2 and 4 kHz. In 2004, Rejali et al conducted a meta-analysis of clinical trials and found that 21.6% of patients with tinnitus reported benefit from *G. biloba* versus 18.4% of patients who reported benefit from a placebo.

A 2004 Cochrane systematic review came to a similar conclusion, reporting that the limited evidence currently available does not support the use of ginkgo in tinnitus; however, the authors also pointed out that if a greater level of understanding and diagnostic accuracy could be reached about the different aetiologies of tinnitus, this may naturally highlight subgroups of patients in whom further controlled trials of *G. biloba* are worth considering (Hilton & Stuart 2004).

Salicylate-induced tinnitus

One in vivo study investigating the effects of ginkgo in salicylate-induced tinnitus found a statistically significant decrease in the behavioural manifestation of tinnitus for ginkgo in doses of 25, 50 and 100 mg/kg/day (Jastreboff et al 1997).

Sudden deafness

Ginkgo extract was as effective as pentoxifylline in the treatment of sudden deafness, according to one randomised, double-blind study (Reisser & Weidauer 2001). Both treatments equally reduced associated symptoms of tinnitus and produced the same effects on the return to normal of speech discrimination. Subjective assessment suggested that

G. biloba extract was more beneficial than pentoxifylline. EGb 761 (240 mg/day) has also been shown to accelerate and secure recovery of acute idiopathic sudden sensorineural hearing loss, observable within 1 week of treatment under randomised double-blind test conditions (Burschka et al 2001).

Commission E approves the use of standardised ginkgo extract in these conditions when of vascular origin (Blumenthal et al 2000).

Macular degeneration, glaucoma and retinopathy

With regard to these ophthalmological conditions, ginkgo has numerous properties that should theoretically make it a useful treatment, such as increasing ocular blood flow, antioxidant and platelet-activating factor inhibitor activity, NO inhibition and neuroprotective abilities.

Macular degeneration

Although some positive evidence exists, a 2000 Cochrane review has suggested that, overall, there is insufficient evidence currently available to conclude that *G. biloba* treatment is effective in macular degeneration, with further testing required (Evans 2000).

Glaucoma

With regard to glaucoma, the little research conducted so far appears promising.

Researchers using colour Doppler imaging have observed significantly increased end-diastolic velocity in the ophthalmic artery after treatment with EGb (120 mg/day) in a placebo-controlled, randomised, crossover study (Chung et al 1999). A randomised, double-blind, crossover study found that EGb 761 (120 mg/day) taken for 4 weeks produces positive effects in normal tension glaucoma (Quaranta et al 2003). Furthermore, ginkgo treatment did not significantly alter intraocular pressure, blood pressure or heart rate and was well tolerated.

Chloroquine retinopathy

In vivo tests using electroretinography have identified protective effects against the development of chloroquine-induced retinopathy using *G. biloba* (Droy-Lefaix et al 1992). This has been observed in both acute and chronic chloroquine toxicity of the retina (Droy-Lefaix et al 1995).

Prevention of altitude sickness

Eight clinical studies have investigated *G. biloba* as prophylactic treatment against altitude sickness (Chow et al 2005, Gertsch et al 2002, 2004, Leadbetter & Hackett 2003, Maakestad et al 2001, Moraga et al 2003, 2007, Roncin et al 1996).

The first study was conducted by Roncin et al (1996). It involved 44 subjects and found that a dose of 160 mg/day taken for 5 days as prophylactic treatment resulted in 0% of subjects developing the cerebral symptoms of acute mountain sickness versus 41% of subjects in the placebo group, whereas only three subjects (13.6%) in the EGb 761 group developed respiratory symptoms of acute mountain sickness (AMS), 18 (81.8%) in the placebo group developed these symptoms. Besides effectively preventing AMS for moderate altitude (5400 m), the treatment also decreased vasomotor disorders of the extremities. In 2001, Maakestad et al reported on a randomised, double-blind trial of *G. biloba* (120 mg twice daily starting 5 days before ascent) compared to placebo for the prevention of AMS in 40 college students who underwent rapid ascent from 1400 to 4300 m. Using the Lake Louise Symptoms (LLS) score and Environmental Symptoms Questionnaire as outcomes, *G. biloba* was shown to significantly reduce the incidence of AMS compared to placebo. A year later, a double-blind study also produced positive results for *G. biloba* 180 mg/day started 24 hours before rapid ascent from sea level to 4205 m (Gertsch et al 2002).

In subsequent years, some researchers compared ginkgo to acetazolamide. In 2003, two studies, which produced conflicting results, were published. Moraga et al (2003) compared prophylaxis with *G. biloba* (80 mg twice daily) versus acetazolamide (250 mg twice daily) versus placebo, which was started 24 hours before rapid ascent to 3700 m. Of 32 subjects enrolled, none of those in the *G. biloba* group developed AMS compared with 35% of those in the acetazolamide group and 54% of those receiving placebo. Alternately, ginkgo (120 mg twice daily) started 3 days before ascent produced no significant effects when compared to placebo or acetazolamide in a randomised, double-blind study by Leadbetter and Hackett (2003). The study involved 59 subjects who experienced a rapid ascent to 4300 m. Negative results were also obtained by Gertsch et al (2004) and Chow et al (2005). The largest negative study involved 487 healthy Western hikers (Gertsch et al 2004). It compared the effects of ginkgo (60 mg three times daily), acetazolamide (250 mg), combined acetazolamide and ginkgo, and placebo. Participants took at least 3–4 doses before ascent above 4000 m in the Nepal Himalayas. The incidence of acute mountain sickness was 34% for placebo, 12% for acetazolamide, 35% for ginkgo and 14% for combined ginkgo and acetazolamide. Chow et al conducted a smaller study of 57 healthy unacclimatised subjects using a randomised, placebo-controlled design. Subjects were taken to an elevation of 3800 m within 24 h, with acetazolamide producing significantly better effects than ginkgo or placebo using the Lake Louise Acute Mountain Sickness Scoring System. Subjects receiving ginkgo were as likely as placebo to experience acute mountain sickness, whereas acetazolamide was protective.

The most recent study was published in 2007 and tested a different type of treatment regimen that produced significant benefits. The placebo-controlled study of 36 people found that pretreatment followed by continued treatment with *G. biloba* prevented acute mountain sickness (AMS) and was significantly more effective than acetazolamide (Moraga et al 2007). Volunteers were given placebo, acetazolamide (250 mg per dose) or ginkgo (80 mg per dose) every 12 hours starting 24 hours before ascending and continued throughout the 3-day stay at high altitude. Not a single person

treated with ginkgo experienced AMS, compared with 36% taking acetazolamide and 54% taking placebo. Whilst ginkgo did not alter arterial oxygen saturation compared to acetazolamide, a marked increased saturation in arterial oxygen was seen in comparison with the placebo group.

Premenstrual syndrome (PMS)

A randomised, double-blind study evaluating the effects of EGb 761 in treating congestive symptoms of PMS in a group of 165 women found that treatment over two menstrual cycles (from day 16 until day 5 of the next cycle) was successful. Treatment was particularly effective in reducing breast symptoms, although neuropsychological symptoms were also alleviated (Tamborini & Taurelle 1993).

Vitiligo

A dose of 120 mg/day ginkgo extract significantly stopped active progression of depigmentation in slow-spreading vitiligo and induced repigmentation in some treated patients under double-blind, placebo-controlled study conditions (Parsad et al 2003). Although the mechanism of action responsible is unknown, antioxidant activity is thought to be important.

Asthma

Ginkgo shows promise as a treatment for asthma, according to studies using a mouse model of asthma and two clinical studies.

Ginkgo significantly reduced airway hyperreactivity, improved clinical symptoms and pulmonary function in asthmatic patients in one placebo-controlled study (Li et al 1997). Platelet-activating factor inhibitor, antioxidant and anti-inflammatory activities are likely to be involved.

Reduced airway inflammation was reported in another study of 75 asthma patients, which compared the effects of fluticasone propionate with fluticasone propionate plus ginkgo (Tang et al 2007b). The addition of ginkgo to treatment resulted in a significant decrease in the infiltration of inflammatory cells such as eosinophils and lymphocytes in the asthmatic airway and relieved airway inflammation.

Babayigit et al used a mouse model of asthma to evaluate the effects of ginkgo on lung histology (Babayigit et al 2008). Treatment with ginkgo was found to significantly improve the number of goblet cells, mast cells, thicknesses of epithelium, and basement membrane compared to placebo, indicating that active treatment improved all established chronic histological lung changes except smooth muscle thickness.

Sexual dysfunction

Due to its vasodilatory effects, ginkgo has been used in the management of sexual dysfunction in cases where compromised circulation is suspected. One open study has been conducted with subjects experiencing sexual dysfunction associated with antidepressant use (Cohen & Bartlik 1998).

Ginkgo extract (average dose 209 mg/day) was found to be 84% effective in treating antidepressant-induced sexual dysfunction, predominantly caused by selective serotonin reuptake inhibitor (SSRI), in a study of 63 subjects (Cohen & Bartlik 1998). A relative success rate of 91% was observed for women, compared with 76% for men, and a positive effect was reported on all four phases of the sexual response cycle: desire, excitement (erection and lubrication), orgasm and resolution. Although this was an open trial, the results are encouraging when one considers that the placebo effect is about 25% from past randomised trials of Federal Drug Administration (FDA)-approved medications for erectile dysfunction (Moyad 2002).

More recently, a small, triple-blind (investigator, patient, statistician), randomised, placebo-controlled, trial of *G. biloba* (240 mg/day for 12 weeks) was undertaken with 24 subjects experiencing sexual impairment caused by antidepressant drugs (Wheatley 2004). The authors report some spectacular individual responses in both groups, but no statistically significant differences, and no differences in side effects.

Meston et al (2008) conducted two studies of women with sexual dysfunction (Meston et al 2008). The first was a single-dose, placebo-controlled study using 300 mg ginkgo extract, which produced a small but significant facilitatory effect on physiological, but not subjective, sexual arousal in 99 sexually dysfunctional women. The second study investigated long-term use of ginkgo (300 mg/day) over 8 weeks, which found that herbal treatment combined with sex therapy significantly increased sexual desire and contentment compared to placebo or ginkgo as sole treatment.

Parkinson's disease

There is great interest in the application of safe substances, such as *G. biloba*, in neurodegenerative diseases such as Parkinson's disease because of their neuroprotective and mitochondrial protective effects. Currently, investigation with ginkgo is limited to animal studies of experimentally induced Parkinson's disease, which have shown it to afford some protection against neuronal loss (Ahmad et al 2005, Kim et al 2004).

OTHER USES

G. biloba is used for many other indications, including improving connective tissue conditions such as haemorrhoids, common allergies, reducing the effects of exposure to radiation and to prevent some of the complications associated with diabetes. In the UK and other European countries, the cardioprotective effects of EGb 761 in myocardial ischaemia and reperfusion are currently being investigated in preclinical studies.

Adjunct in cancer treatment

As a herb with significant antioxidant and neuroprotective activities, ginkgo has been used to reduce the toxic side effects of some chemotherapeutic drugs. Evidence from in vivo studies demonstrates protective effects against nephrotoxicity induced by cisplatin and cardiotoxicity induced by doxorubicin (Naidu et al 2002, Ozturk et al 2004).

More recently, *G. biloba* extract (EGb 761) given intraperitoneally as 200 mg/kg, was found to protect against cisplatin-induced ototoxicity in an animal model (Huang et al 2007). Another in vivo study showed that *G. biloba* extract prevented adriamycin-induced hyperlipidaemic nephrotoxicity and was associated with a decrease in oxidative stress and total NO levels of renal tissues (Abd-Ellah & Mariee 2007).

Clinical trials are not yet available to determine its effectiveness in practice.

Cancer prevention

A 2006 review puts forward the case that *G. biloba* should be more widely used as a safe preventative agent for reducing cancer incidence. This recommendation is based on results from numerous in vitro and experimental studies showing that ginkgo affects many factors associated with the incidence and mortality of cancer (Eli & Fasciano 2006).

Multiple sclerosis

Multiple sclerosis (MS) is a chronic demyelinating neurological disease afflicting young and middle-aged adults, resulting in problems with coordination, strength, cognition, affect and sensation. Two clinical studies have investigated whether ginkgo treatment may help reduce some of these impairments.

Johnson et al (2006) conducted a randomised, double-blind study which compared the effects of ginkgo (EGb 761; 240 mg/day) to placebo on depression, anxiety, fatigue, symptom severity and functional performance using validated measures for each outcome (Johnson et al 2006). Twenty-two people with MS were enrolled in the study. Significantly, more people administered ginkgo showed improvement on four or more measures with improvements associated with significantly larger effect sizes on measures of fatigue, symptom severity and functionality. The ginkgo group also exhibited less fatigue at follow-up compared with the placebo group and treatment was well tolerated with no side effects or adverse effects reported.

The cognitive function of people with multiple sclerosis significantly improved after 12 weeks of treatment with *G. biloba* extract (120 mg twice a day), according to a randomised, double-blind, placebo-controlled trial (Lovera et al 2007). A treatment effect trend, limited to the Stroop test, indicated that ginkgo treatment may have an effect on cognitive domains assessed by this test, such as susceptibility to interference and mental flexibility. People with greater cognitive impairment at the start of the study experienced more improvement with treatment than higher functioning people. No serious drug-related side effects occurred.

Schizophrenia — adjunctive treatment

G. biloba given as an adjunct to the atypical antipsychotic medicine, clozapine, in the treatment of refractory schizophrenia was shown to enhance drug effects on negative symptoms according to a placebo-controlled study involving 42 patients with chronic, treatment-resistant schizophrenia (Doruk et al 2008). Ginkgo was used at a dose of 120 mg/day for 12 weeks.

DOSAGE RANGE

The recommended dose varies, depending on indication and condition treated.

General guide

- Dried herb: 9–10 g/day.
- 120–240 mg of a 50:1 standardised extract daily in divided doses (40 mg extract is equivalent to 1.4–2.7 g leaves).
- Fluid extract (1:1): 0.5 mL three times daily.

According to clinical studies

- Asthma: 40 mg three times daily.
- Dementia and memory impairment: 120–240 mg standardised extract daily in divided doses.
- Intermittent claudication, vertigo: 120–320 mg standardised extract daily in divided doses.
- Normal tension glaucoma: 120 mg standardised extract daily.
- Multiple sclerosis — to improve cognitive function and mood: 120 mg twice daily.
- PMS: 80 mg twice daily, starting on the 16th day of the menstrual cycle until the 5th day of the next cycle.
- Prevention of altitude sickness: 160 mg standardised extract daily, starting 5 days prior to ascent or ginkgo (80 mg per dose) every 12 hours, starting 24 hours before ascending and continuing throughout stay at high altitude.
- Schizophrenia: as an adjunct to clozapine in refractory cases: 120 mg daily.
- Raynaud's syndrome: 360 mg/day divided into three doses.
- Sexual dysfunction associated with antidepressant drugs: 200 mg standardised extract daily.
- Sexual dysfunction (women): 300 mg daily in conjunction with sex therapy.
- Vitiligo: 120 mg standardised extract daily.

Although some studies report positive effects after 4–6 weeks' continual use, a trial of at least 12 weeks is recommended in chronic conditions.

ADVERSE REACTIONS

In most placebo-controlled studies, there is no difference between the side effect incidence with ginkgo and placebo. Standardised ginkgo leaf extracts have been used safely in trials lasting from several weeks to up to 6 years.

In a few cases (less than 0.001%), gastrointestinal upset, headaches and dizziness were reported. It does not appear to alter heart rate and blood pressure, change cholesterol and triglyceride levels or increase intraocular pressure in clinical studies (Chung et al 1999).

At least 10 clinical studies have found no significant effect on bleeding or platelets; however, rare case reports of subarachnoid haemorrhage, subdural haematoma, intracerebral haemorrhage, subphrenic haematoma, vitreous haemorrhage and postoperative bleeding have been reported.

Crude ginkgo plant parts that may contain concentrations of 5 ppm of the toxic ginkgolic acid

constituents should be avoided, as they can induce severe allergic reactions.

SIGNIFICANT INTERACTIONS

Adriamycin

Studies with an animal model indicate that ginkgo extract EGb 761 reduces the hyperlipidaemia and proteinuria associated with adriamaycin-induced nephropathy, which might be beneficial to enhance the therapeutic index of adriamycin (Abd-Ellah & Mariee 2007). Clinical trials have not been conducted to confirm the activity.

Antidepressant drugs

Ginkgo may reduce the sexual dysfunction side effects of these drugs and improve sleep continuity; however, results from clinical studies are mixed — possible beneficial interaction.

Bleomycin

Studies with an animal model indicate that ginkgo extract EGb 761 reduces oxidative stress induced by bleomycin. This may improve drug tolerance; however, clinical studies have not yet been conducted to test this further (Erdogan et al 2006).

Cholinergic drugs

Cholinergic activity has been identified for ginkgo; therefore, combined use may theoretically increase drug activity — observe patients using this combination, although the effects may be beneficial when used under supervision.

Cisplatin

As a herb with significant antioxidant activity, ginkgo has also been employed as a means of reducing the nephrotoxic effects of cisplatin, a use supported by two in vivo studies (Gulec et al 2006, Ozturk et al 2004). Other researchers using animal models have indicated that ginkgo may protect against cisplatin-induced ototoxicity (Huang et al 2007). Clinical trials are required to confirm significance — adjunctive use may be beneficial when used under professional supervision.

Clinical note — Does Ginkgo biloba cause significant bleeding and does it interact with warfarin?

The current body of evidence casts doubt on the clinical significance of the proposed interaction between warfarin and ginkgo, revealing that there is little evidence from controlled studies to demonstrate significant platelet inhibition, bleeding or changes to international normalised ratio (INR) with use of ginkgo (especially EGb 761 or phytochemically similar extracts).

To date five clinical trials have been published in peer-reviewed journals which demonstrate that *G. biloba* does not have a significant effect on platelet function, two studies showing no interaction with warfarin, one study showing no interaction with aspirin and a further study showing no interaction with clopidogrel (Aruna & Naidu 2007, Bal Dit et al 2003, Beckert et al 2007, Carlson et al 2007, Engelsen et al 2003, Gardner et al 2007, Jiang et al 2005, Kohler et al 2004). Studies have included young healthy volunteers and older adults, using doses up to 480 mg/day of ginkgo and time frames up to 4 months.

The first controlled study was published in 2003. Bal Dit et al conducted a double-blind, randomised, placebo-controlled study of 32 young healthy volunteers to evaluate the effect of three doses of *G. biloba* extract (120, 240 and 480 mg/day for 14 days) on haemostasis, coagulation and fibrinolysis (Bal Dit et al 2003). This escalating dose study found no effect on platelet function or coagulation for any dose tested. A year later, results from a larger randomised, placebo-controlled, crossover study that produced similar results was published (Kohler et al 2004). The study by Kohler, Funk and Keiser investigated the effects of ginkgo (2 × 120 mg/day EGb 761) on 29 different coagulation and bleeding parameters. Once again, no evidence of inhibition of blood coagulation and platelet aggregation was detected. In Australia, Jiang et al investigated the interaction between warfarin and *G. biloba* using a randomised, crossover study design (Jiang et al 2005). The study of 12 healthy males found no evidence that INR or platelet aggregation was affected by *G. biloba*. Engelsen, Nielson and Hansen also found no evidence of an interaction between *G. biloba* and warfarin under double-blind, placebo-controlled trial conditions (Engelsen et al 2003). The study involved patients stable on long-term warfarin and reported no changes to INR values.

In 2007, four more studies were published. Carlson et al conducted a study of 90 older adults (65–84 years) who were randomly assigned to placebo or a *G. biloba*-based supplement (160 mg/day) for 4 months (Carlson et al 2007). No evidence of alteration to platelet function was seen at this dose. Beckert et al conducted a smaller trial of 10 volunteers who were administered ginkgo for 2 weeks, after which in vivo platelet function was quantified using the PFA-100 assay (Beckert et al 2007). The study used aspirin as a control agent and found that platelet function was not affected by *G. biloba*, but was markedly inhibited by the administration of aspirin. No clinically or statistically significant differences were seen in a randomised, double-blind, placebo-controlled trial, which investigated the effects of *G. biloba* (EGb 761, 300 mg/day) on several measures of platelet aggregation among 55 older adults (age 69 ± 10 years) also consuming 325 mg/day aspirin (Gardner et al 2007). Reports of bleeding or bruising were infrequent and similar for both study groups. Finally, a study of 10 healthy volunteers investigated the effects of two different doses of *G. biloba* (120 mg and 240 mg) taken together with clopidogrel (75 mg) (Aruna & Naidu 2007). Platelet inhibition with the combination of *G. biloba* and clopidogrel was not statistically significant, compared with individual doses of drugs.

Clozapine
Ginkgo may enhance the effects of clozapine on negative affect in refractory schizophrenic patients, according to a placebo-controlled study (Doruk et al 2008) — beneficial interaction.

Doxorubicin
In vivo research suggests that ginkgo can prevent doxorubicin-induced cardiotoxicity suggesting a potentially beneficial interaction, although no human studies are available to confirm clinical significance (Naidu et al 2002).

Haloperidol
In three clinical trials, the effectiveness of haloperidol was enhanced when co-administered with 360 mg of ginkgo daily (Chavez et al 2006) — beneficial interaction under supervision.

Platelet inhibitor drugs
Due to its platelet-activating factor antagonist activity, *G. biloba* may theoretically enhance the effects of these drugs and increase risk of bruising or bleeding; however, evidence from recent clinical trials have cast doubt on the clinical significance of this activity.

Valproate, dilantin, depakote
There is a report of two patients using valproate who experienced seizures with ginkgo use (Chavez et al 2006). There is also a report of a patient taking Dilantin and Depakote and ginkgo, together with other herbal medicines, who suffered a fatal breakthrough seizure, with no evidence of non-compliance with anticonvulsant medications (Kupiec & Raj 2005). The autopsy report revealed subtherapeutic serum levels for both anticonvulsants, Depakote and Dilantin; however, it is uncertain whether effects can be attributed to ginkgo — observe patient taking ginkgo with these medicines.

Warfarin
Theoretically, ginkgo may increase bleeding risk when used together with warfarin; however, evidence from controlled clinical studies do not support this conclusion and have failed to identify any clinically significant pharmacodynamic or pharmacokinetic interaction. This conclusion is supported by a recent systematic review (Bone 2008) — observe.

CONTRAINDICATIONS AND PRECAUTIONS
If unusual bleeding or bruising occurs, stop use immediately. Although new clinical evidence suggests that *G. biloba* does not affect clotting times, it may be prudent to suspend use for 1 week prior to major surgery in at-risk populations.

Cerebral haemorrhage and epilepsy
Rare case reports have suggested that ginkgo should be used with caution in people with known risk factors for cerebral haemorrhage and epilepsy until further investigation can clarify its safety (Benjamin et al 2001, Granger 2001, Vale 1998).

PREGNANCY USE
Insufficient reliable evidence is available to determine safety.

PATIENTS' FAQs
What will this herb do for me?
Ginkgo is a very popular herbal treatment that increases peripheral circulation, beneficially influences brain chemicals, protects nerve cells from damage, and may stimulate immune function and reduce inflammation. Scientific evidence has shown that it may improve cognitive function in people with mild-to-moderate cognitive impairment when used long term in sufficient dosage, but it is less successful in people with normal function. It may also improve some aspects of memory in younger people when used short term. Ginkgo may improve symptoms of intermittent claudication and be useful in treating chilblains, PMS, vitiligo, preventing altitude sickness and seasonal affective disorder and possibly sexual dysfunction such as impotence. If taken long term, it does not protect against the development of dementia in the future and it does not effectively treat tinnitus.

PRACTICE POINTS/PATIENT COUNSELLING
- *G. biloba* is a complex herb that contains many different active constituents and works by means of multiple mechanisms. Therefore, it has applications in many varied conditions.
- Overall, the evidence suggests that oral ginkgo extract may improve cognitive function in people with mild-to-moderate cognitive impairment, but it is less successful in people with normal cognitive function.
- Long-term use does not appear to protect against the development of dementia and it is ineffective in treating tinnitus.
- It may be an effective treatment in peripheral vascular diseases such as intermittent claudication; however, study findings are not always consistent. Due to the herb's inherent safety, a therapeutic trial may be useful in practice to determine an individual's response.
- Some positive evidence exists for PMS, sudden deafness, Raynaud's syndrome, preventing altitude sickness, improving cognitive function in multiple sclerosis and depression when associated with cognitive decline.
- Preliminary evidence suggests a possible role as adjunctive therapy for patients receiving chemotherapy, to reduce drug toxicity side effects.
- Largely based on the herb's physiological actions, ginkgo is also used to treat chilblains, haemorrhoids, prevent macular degeneration, glaucoma, sexual dysfunction, impotence, allergies and asthma and improve wellbeing.
- The form of ginkgo most often tested and used is a preparation known as EGb 761, which is standardised to 24% ginkgo flavonol glycosides and 6% terpene lactones.
- Overall, *G. biloba* is a very safe herb and is extremely well tolerated.

When will it start to work?

This will depend on the condition treated and the dose used. Generally, *G. biloba* is a slow-acting herb that can take anywhere from 4 weeks to 3 months to exert maximal effects.

Are there any safety issues?

Ginkgo has been extensively studied and appears to be extremely safe with virtually no side effects in healthy people. Some contraindications and interactions are possible, so it is recommended that it should be taken under professional supervision.

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Ginseng — Korean

HISTORICAL NOTE *Gin* refers to man and *seng* to essence in Chinese, whereas *Panax* is derived from the Greek word *pan* (all) and *akos* (cure), referring to its use as a cure-all. Ginseng is a perennial herb native to Korea and China and has been used as a herbal remedy in eastern Asia for thousands of years. It is considered to be the most potent Qi or energy tonic in Traditional Chinese Medicine (TCM). Modern indications include low vitality, poor immunity, cancer, cardiovascular disease and enhancement of physical performance and sexual function. However, a recent systematic review of randomised controlled trials (RCTs) found that the efficacy of ginseng root extract could not be established beyond doubt for any of these indications (Coon & Ernst 2002).

COMMON NAME
Korean ginseng

OTHER NAMES
Ren shen (Mandarin), red ginseng, white ginseng

BOTANICAL NAME/FAMILY
Panax ginseng C.A. Meyer (family Araliaceae)

It should be differentiated from *P. aquifolium* (American ginseng), *P. notoginseng* (Tien chi, pseudo-ginseng), *Eleutherococcus senticosis* (Siberian ginseng) and other ginsengs.

PLANT PART USED
Main and lateral roots. The smaller root hairs are considered an inferior source. There are two types of preparations produced from ginseng: white ginseng, which is prepared by drying the raw herb, and red ginseng, prepared by steaming before drying. Cultivated ginseng differs from wild ginseng, and plants from different countries or regions may also differ greatly. Processing of the crude herb to produce red ginseng appears to increase its potency. Steaming has been shown to alter the composition of the ginsenosides; for example, steaming produces the active 20(S)-ginsenoside-Rg(3) (Matsuda et al 2003) and makes certain ginsenosides more cytotoxic (Park et al 2002a).

The British Herbal Pharmacopoeia (1983) stipulates that ginseng should contain not less than 20% solids (70% ethanol). The German Pharmacopoeia requires not less than 1.5% total ginsenosides, calculated as ginsenoside Rg 1.

Chewing gums containing ginseng saponins have also been developed and demonstrate therapeutic effects in some trials (Ding et al 2004).

CHEMICAL COMPONENTS
The most characteristic compounds in the ginseng roots are the ginsenosides, and most biological effects have been ascribed to these compounds. The ginsenosides are dammarane saponins and can be divided into two classes: the protopanaxatriol class consisting primarily of Rg1, Rg2, Rf and Re and the protopanaxadiol class consisting primarily of Rc, Rd, Rb1 and Rb2. Ginseng also contains other saponins, polysaccharides, amino acids (in particular glutamine and arginine) (Kuo et al 2003), essential oils and other compounds. Three new sesquiterpene hydrocarbons have also recently been isolated from the essential oil: panaxene, panaginsene and ginsinsene (Richter et al 2005).

Ginsenosides Rh1, Rh2 and Rg3 are obtained from red ginseng as artifacts produced during steaming. It is likely that ginsenoside is actually a prodrug that is converted in the body by intestinal bacterial deglycosylation and fatty acid esterification into an active metabolite (Hasegawa 2004), and therefore, extrapolation from in-vitro studies or studies in which ginseng or isolated constituents were given by injection must be made very cautiously.

Commercial ginseng preparations are variable in quality. An analysis of 50 products sold in 11 countries shows that there is a large variation in the concentration of ginsenosides (from 1.9 to 9.0%). Some products were even found to be void of any specific ginsenosides. Some ginseng products have also been discovered to be contaminated with ephedrine. Therefore, it is essential that only quality ginseng products be used (Cui et al 1994). Although the root hairs have a higher level of total ginsenosides than the main root, the main and lateral roots are the preferred medicinal parts. In all probability, it is the ratio of ginsenosides that is

important and other important compounds are also active.

MAIN ACTIONS

Adaptogen

The pharmacological effects of ginseng are many and varied, contributing to its reputation as a potent adaptogen. The adrenal gland and the pituitary gland are both known to have an effect on the body's ability to respond to stress and alter work capacity (Filaretov et al 1988), and ginseng is thought to profoundly influence the hypothalamic–pituitary–adrenal axis (Kim et al 2003c). The active metabolites of protopanaxadiol and protopanaxatriol saponins reduce acetylcholine-induced catecholamine secretion in animal models (Tachikawa & Kudo 2004, Tachikawa et al 2003) and this may help to explain the purported antistress effects of ginseng.

Ginseng has been shown in numerous animal experiments to increase resistance to a wide variety of chemical, physical and biological stressors. Ginseng extract or its isolated constituents have been shown to prevent immunosuppression induced by cold water swim stress (Luo et al 1993) and to counter stress-induced changes from heat stress (Yuan 1989), food deprivation (Lee et al 1990), electroshock (Banerjee & Izquierdo 1982) and radiation exposure (Takeda et al 1981). As there are more than 1500 studies on ginseng and its constituents, it is outside the scope of this monograph to include all studies, so we have attempted to include those studies most relevant to the oral use of ginseng.

Animal models suggest that ginseng is most useful for chronic rather than acute stress, significantly reducing elevated scores on ulcer index, adrenal gland weight, plasma glucose, triglycerides, creatine kinase activity and serum corticosterone during chronic stress (Rai et al 2003).

(Refer to the Siberian ginseng monograph for more information about adaptogens and allostasis.)

Cardiovascular effects

According to in vitro and animal studies, ginseng may benefit the cardiovascular system 'through diverse mechanisms, including antioxidant, modifying vasomotor function, reducing platelet adhesion, influencing ion channels, altering autonomic neurotransmitter release, improving lipid profiles' and glycaemic control (Zhou et al 2004).

Antihypertensive

Red ginseng has been used as an antihypertensive agent in Korea, but its clinical effect is unclear despite several in-vivo and in-vitro experimental studies. Recent preliminary data suggest that the antihypertensive effects may be partly attributed to an angiotensin-converting enzyme (ACE) inhibitory effect demonstrated by *P. ginseng* extract in vitro (Persson et al 2006). These effects were additive to the traditional ACE inhibitor enalapril.

A study of isolated muscle preparations of animal heart and aorta with an alcohol-based extract of ginseng suggests that the hypotensive effect of ginseng is associated with a direct inhibition of myocardial contractility due to a reduction of calcium ion influx into cardiac cells, as well as the inhibition of catecholamine-induced contractility of vascular smooth muscles (Hah et al 1978).

In a prospective, randomised, double-blind, placebo-controlled study of 30 healthy adults, 200 mg ginseng extract given for 28 days was found to increase the QTc interval and decrease diastolic blood pressure 2 h after ingestion on the first day of therapy. These changes, however, were not thought to be clinically significant (Caron et al 2002).

Antiplatelet

Although reports from recent in-vitro and in vivo assays claim that *P. ginseng* is not one of the herbs that contributes to the antiplatelet effects of a Korean combination formula known as Dae-Jo-Hwan (Chang et al 2005), a number of studies have found that several ginsenosides inhibit platelet aggregation. Panaxynol has been shown to inhibit platelet aggregation induced by adenosine disphosphate, collagen and arachidonic acid. Panaxynol and ginsenosides Ro, Rg and Rg2 inhibit rabbit platelets while panaxynol prevented platelet aggregation and thromboxane formation (Kuo et al 1990).

Antihyperlipidaemic

Ginsenoside Rb1 has been shown to lower triglyceride and cholesterol levels via cyclic adenosine monophosphate (cAMP) production in the rat liver (Park et al 2002b). *P. ginseng* extract (6 g/day) for 8 weeks resulted in a reduction in serum total cholesterol, triglyceride, low density lipoprotein (LDL) and plasma malondialdehyde levels and an increase in high density lipoprotein (HDL) (Kim & Park 2003) in eight males. Ginseng has also been reported to decrease hepatic cholesterol and triglyceride levels in rats, indicating a potential use of ginseng in the treatment of fatty liver (Yamamoto et al 1983).

Other cardiovascular effects

Ginsenoside Rb2 has been shown to enhance the fibrinolytic activity of bovine aortic endothelial cells (Liu 2003). In animal studies, ginseng inhibits cardiomyocyte apoptosis induced by ischaemia and reperfusion (Zeng et al 2004) and the crude saponins have been shown to reduce body weight, food intake and fat content in rats fed a high-fat diet (Kim et al 2005a). In-vitro studies report that an extract of ginseng fruit can promote vascular endothelial cell proliferation, migration, DNA synthesis and vascular endothelial growth factor mRNA expression, suggesting an effect on the genesis and development of new vessels in the ischaemic myocardium (Lei et al 2008).

Gastrointestinal

Hepatorestorative

Oral administration of Korean red ginseng (250 and 500 mg/kg) on liver regeneration has been investigated in 15 dogs with partial hepatectomy. All haematological values except leucocyte counts

were within normal ranges for 3 days postoperatively. The levels of aspartate transaminase (AST and alanine aminotransferase (ALT) in the ginseng groups were significantly decreased compared with those in the control group ($P < 0.05$). The numbers of degenerative cells and areas of connective tissue were significantly decreased in the livers of the dogs treated with ginseng ($P < 0.01$) (Kwon et al 2003).

Anti-ulcerative

Ginseng has been shown in several studies to protect against ulceration. Among the hexane, chloroform, butanol and water fractions, the butanol fraction of a ginseng extract has been shown to be the most potent inhibitor of HCl-induced gastric lesions and ulcers induced by aspirin, acetic acid and Shay (ulcer induced by pylorus ligation). The butanol fraction showed significant increase in mucin secretion, and inhibited malondialdehyde and H^+/K^+ATPase activity in the stomach. These results indicate that the effectiveness of ginseng on gastric damage might be related to inhibition of acid secretion, increased mucin secretion and antioxidant properties (Jeong 2002). Furthermore, inhibition of *Helicobacter pylori*-stimulated 5-lipoxygenase activity may have a beneficial effect on *H. pylori*-associated gastric inflammation (Park et al 2007).

Effects on peristalsis

Ginseng root extract and its components, ginsenoside Rb1(4) and ginsenoside Rd(7), have been shown to significantly ameliorate chemically induced acceleration of small intestinal transit in vivo. The test results suggest that the protective mechanism involves both an inhibitory effect on the cholinergic nervous system and a direct suppressive effect on intestinal muscles (Hashimoto et al 2003).

Anti-inflammatory

Both a crude and a standardised extract (G115) of ginseng varying in saponin concentrations have been found to protect against muscle fibre injury and inflammation after eccentric muscle contractions in rats on a treadmill. The oral ginseng extracts significantly reduced plasma creatine kinase levels by about 25% and lipid peroxidation by 15%. Certain markers of inflammation were also significantly reduced (Cabral de Oliveira et al 2001). In a later study, pretreatment with ginseng extract (3, 10, 100 or 500 mg/kg) administered orally for 3 months to male Wistar rats resulted in a 74% decrease in lipid peroxidation caused by eccentric exercise (Voces et al 2004).

The many and varied effects of ginseng may be partly associated with the inhibition of transcription factor nuclear factor (NF)-kappaB, which is pivotal in the regulation of inflammatory genes. Inhibition of NF-kappaB may reduce inflammation and protect cells against damage.

Topical application of several ginsenosides (Rb1, Rc, Re, Rg1, Rg3) significantly attenuated chemically induced ear oedema in mice. The ginsenosides also suppressed expression of cyclooxygenase-2 (COX-2) and activation of NF-kappaB in the skin. Of the ginsenosides tested, Rg3 was found to be most effective (Surh et al 2002).

Immunomodulation

The immunomodulatory effect of ginseng is based on the production of cytokines, activation of macrophages, stimulation of bone marrow cells and stimulation of inductible nitric oxide synthase (iNOS), which produces high levels of NO in response to activating signals from Th1-associated cytokines and plays an important role in cytotoxicity and cytostasis (growth inhibition) against many pathogenic microorganisms. In addition to its direct effector function, NO serves as a potent immunoregulatory factor.

Ginseng enhances interleukin (IL)-12 production and may therefore induce a stronger Th1 response, resulting in improved protection against infection from a variety of pathogens (Larsen et al 2004), including *Pseudomonas aeruginosa* lung infection in animal models (Song et al 2005), although other studies suggest that it may also assist in the correction of Th1-dominant pathological disorders (Lee et al 2004a).

Ginseng polysaccharides have been shown to increase the cytotoxic activity of macrophages against melanoma cells, increase phagocytosis and induce the levels of cytokines, including tissue necrosis factor (TNF)-alpha, IL-1-beta, IL-6 and interferon-gamma in vitro (Shin et al 2002). Ginseng has been shown to be an immunomodulator and to enhance antitumour activity of macrophages in vitro (Song et al 2002). Ginseng has also been shown significantly to enhance natural killer (NK) function in an antibody-dependent cellular cytotoxicity of peripheral blood mononuclear cells in vitro (See et al 1997).

Incubation of macrophages with increasing amounts of an aqueous extract of ginseng showed a dose-dependent stimulation of iNOS. Polysaccharides isolated from ginseng showed strong stimulation of iNOS, whereas a triterpene-enriched fraction from an aqueous extract did not show any stimulation. As NO plays an important role in immune function, ginseng could modulate several aspects of host defence mechanisms due to stimulation of the iNOS (Friedl et al 2001).

Ginseng promotes the production of granulocytes in the bone marrow (granulocytopoiesis). The ginseng saponins have been shown to directly and/or indirectly promote the stromal cells and lymphocytes to produce human granulocyte–macrophage colony-stimulating factor (GM-CSF) and other cytokines and induce bone marrow haemopoietic cells to express GM-CSF receptors, leading to a proliferation of human colony-forming units for granulocytes and macrophages in vitro (Wang et al 2003).

Ginseng polysaccharides have been shown to have potent antisepticaemic activity by stimulating macrophages and helping modulate the reaction against sepsis induced by *Staphylococcus aureus*. Ginseng polysaccharides have been shown to reduce the intracellular concentration of *S. aureus* in macrophages in infected animals by 50% compared with

controls. Combination of the ginseng polysaccharides with vancomycin resulted in 100% survival of the animals, whereas only 67 or 50% of the animals survived, respectively, when treated with the ginseng polysaccharides or vancomycin alone (Lim et al 2002a).

According to animal studies, long-term oral administration of ginseng extract may potentiate humoral immune response but suppress spleen cell functions (Liou et al 2005).

Anticancer

Oral intake of standardised *P. ginseng* extract demonstrates a dose-dependent (1, 3 or 10 mg/kg) chemoprotective and antimutagenic effect in animal studies (Panwar et al 2005), and ginsenoside Rg3 has recently been produced as an antiangiogenic anticarcinogenic drug in China (Shibata 2001).

Chemoprotection

Oral administration of red ginseng extracts (1% in diet for 40 weeks) significantly ($P < 0.05$) suppressed spontaneous liver tumour formation in male mice. Oral white ginseng was also shown to suppress tumour promotion in vitro and in vivo (Nishino et al 2001).

Dietary administration of red ginseng in combination with 1,2-dimethylhydrazine suppresses colon carcinogenesis in rats (rats were fed 1% ginseng for 5 weeks). It is thought that the inhibition may be partly associated with inhibition of cell proliferation in the colonic mucosa (Fukushima et al 2001).

Oral administration of 50 mg/kg/day for 4 weeks of a ginseng intestinal metabolite has been shown to partially protect against doxorubicin-induced testicular toxicity in mice. The metabolite significantly ($P < 0.01$) prevented decreases in body weight, spermatogenic activities, serum levels of lactate dehydrogenase and creatine phosphokinase induced by doxorubicin. It also significantly attenuated germ cell injuries (Kang et al 2002).

The methanol extract of red ginseng has been shown to attenuate the lipid peroxidation in rat brain and scavenge superoxides in differentiated human promyelocytic leukaemia (HL-60) cells. Topical application of the same extract, as well as purified ginsenoside Rg3, has been demonstrated to suppress skin tumour promotion in mice. Rg3 also suppresses COX, NF-kappaB and extracellular-regulated protein kinase, which are all involved in tumour promotion (Surh et al 2001).

Pretreatment with oral red ginseng extract significantly reduced the development of cancer from diethylnitrosamine-induced liver cancer nodules in rats (the developmental rate of liver cancer in the experimental group was 14.3% compared with 100% in the control group). When ginseng was given concomitantly with diethylnitrosamine, the hepatoma nodules were smaller than those of the control group, the structure of hepatic tissue was well preserved and the structure of hepatocytes was normal. Ginseng also prolonged the average life span. These findings suggest benefits of ginseng in the prevention and treatment of liver cancer (Wu et al 2001).

Irradiation protection

Ginsenosides and specifically panaxadiol have been shown to have radioprotective effects in mice irradiated with high-dose and low-dose gamma radiation. Jejunal crypts were protected by pretreatment with extract of whole ginseng (50 mg/kg body weight intraperitoneally at 12 and 36 hours before irradiation, $P < 0.005$). Extract of whole ginseng ($P < 0.005$), total saponin ($P < 0.01$) or panaxadiol ($P < 0.05$) administration before irradiation (50 mg/kg body weight IP at 12 and 36 hours before irradiation) resulted in an increase in the formation of the endogenous spleen colony. The frequency of radiation-induced apoptosis in the intestinal crypt cells was also reduced by pretreatment with extract of whole ginseng, total saponin and panaxadiol (Kim et al 2003c).

These radioprotective effects are partly associated with the immunomodulatory effect of ginseng. Ginsan, a purified polysaccharide isolated from ginseng, has been shown to have a mitogenic activity, induce lymphokine-activated killer cells and increase levels of several cytokines. Ginsan reduced mutagenicity in a dose-dependent manner when applied to rats 30 min before or 15 min after 1.5 Gy of gamma irradiation. The radioprotective effect of ginsan has been partly attributed to a reduction in radiation-induced genotoxicity (Ivanova et al 2006). Ginsan has also been found to increase the number of bone marrow cells, spleen cells, granulocyte–macrophage colony-forming cells and circulating neutrophils, lymphocytes and platelets significantly in irradiated mice (Song et al 2003).

One of the causes of radiation damage is lipid peroxidation, which alters lysosomal membrane permeability, leading to the release of hydrolytic enzymes. Ginseng has been shown to markedly inhibit lipid peroxidation and protect against radiation damage in testes of mice (Kumar et al 2003).

Antitumour, antiproliferative, antimetastatic and apoptosis inducing

Stimulation of the phagocytic activity of macrophages may play a role in the anticarcinogenic and antimetastatic activities demonstrated for ginseng in vivo (Shin et al 2004b), and research has continually found tumour-inhibitory effects, especially in the promotion and progression phases (Helms 2004).

Ginsenosides Rg3, Rg5, Rk1, Rs5 and Rs4 have been shown to be cytotoxic to Hep-1 hepatoma cancer cells in vitro. Their 50% growth inhibition concentration (GI50) values were 41, 11, 13, 37 and 13 micromol/L, respectively. Cisplatin had a GI50 of 84 micromol/L in the same assay conditions (Park et al 2002a). Several triterpenoids found in the leaves have also demonstrated cytotoxic activity in vitro (Huang et al 2008).

Constituents in ginseng have also been shown to inhibit proliferation of cancer cells. Panaxytriol isolated from red ginseng was shown to have a significant dose-dependent cytotoxic activity and inhibit DNA synthesis in various tumour cells tested (Kim et al 2002a). Ginsenoside Rg3 has displayed inhibitory activity against human prostate cancer cells in vitro (Liu et al 2000).

Ginsenosides, especially 20(R)-ginsenoside Rg3, have been shown to specifically inhibit cancer cell invasion and metastasis (Shibata 2001), and ginsenoside Rh2 has been shown to inhibit human ovarian cancer growth in mice (Nakata et al 1998). It is likely that the antitumour-promoting activity of Rg3 is mediated through down-regulation of NF-kappaB and other transcription factors (Keum et al 2003).

Oral administration of 20(S)-protopanaxatriol (M4), the main bacterial metabolite of protopanaxatriol-type ginsenosides, has been shown to inhibit melanoma growth in mice, and pretreatment was shown to reduce metastases to the lungs. This effect is thought to be due to stimulation of NK-mediated tumour lysis (Hasegawa et al 2002).

The antimetastatic effects of ginseng are related to inhibition of the adhesion and invasion of tumour cells and also to antiangiogenesis activity. Ginsenosides Rg3 and Rb2 have been shown to significantly inhibit adhesion of melanoma cells to fibronectin and laminin, as well as preventing invasion into the basement membrane in vitro. Other experiments have demonstrated that the saponins exert significant antiapoptotic activity, decreasing the number of blood vessels oriented towards the tumour mass (Mochizuki et al 1995, Sato et al 1994).

Ginseng saponins have also been found to promote apoptosis (programmed cell death) in cancer cells in vitro (Hwang et al 2002).

Neurological

Analgesia

Intraperitoneal administration of ginsenoside Rf has been shown to potentiate opioid-induced analgesia in mice. Furthermore, ginsenosides prevented tolerance to the opiate that was not associated with opioid or GABA receptors (Nemmani & Ramarao 2003).

Neuroprotection

Ginseng saponins have demonstrated dose-dependent neuroprotective activity in vitro and in vivo (Kim et al 2005b). Ginsenosides Rb1 and Rg1 have a partial neurotrophic and neuroprotective role in dopaminergic cell cultures (Radad et al 2004), and Rg3 has been shown to inhibit chemically induced injuries in hippocampal neurons (Kim et al 2002b). Pretreatment with ginsenosides (50 or 100 mg/kg for 7 days) has been shown to be neuroprotective in vivo (Lee et al 2002a). An in-vitro survival assay demonstrated that ginsenosides Rb1 and Rg1 protect spinal cord neurons against damage. The ginsenosides protect spinal neurons from excitotoxicity induced by glutamate and kainic acid, as well as oxidative stress induced by H_2O_2. The optimal doses are 20–40 micromol/L for ginsenosides Rb1 and Rg1 (Liao et al 2002). The lipophilic fraction of ginseng has been shown to induce differentiation of neurons and promote neuronal survival in the rat cortex. The effect is thought to be mediated via protein kinase-C-dependent pathways (Mizumaki et al 2002). In-vitro studies have also suggested a benefit for ginseng in hypoxia-induced neuronal injury including ischaemia, trauma and degenerative diseases (Park et al 2007). Beneficial effects have yet to be demonstrated in clinical trials.

It has been suggested that the neuroprotective effects of ginseng against hypoperfusion/reperfusion-induced brain injury demonstrated in animal models suggest a potential for use in cardiovascular (CVD) (Shah et al 2005).

Cognitive function

Following oral consumption, the active metabolites of protopanaxadiol saponins may reactivate neuronal function in Alzheimer's disease according to in-vivo evidence (Komatsu et al 2005). Ginseng also enhances the survival of newly generated neurons in the hippocampus, which may contribute to the purported benefits of ginseng for improving learning tasks (Qiao et al 2005).

Anticonvulsant

Pretreatment (30 min) with 100 mg/kg ginseng significantly protected rats against pentylenetetrazole-induced seizures (Gupta et al 2001).

Antidiabetic

Hypoglycaemic/antihyperglycaemic effects

Human and animal studies have found American ginseng to lower blood glucose level (Vuksan et al 2000a, 2000b, 2000c, 2001a, 2001b). Results for Korean ginseng are less consistent (Sievenpiper et al 2003, 2004). Both ginseng root and berry (150 mg/kg) have been shown to significantly decrease fasting blood glucose levels in hyperglycaemic rats (Dey et al 2003). Intraperitoneal administration of glycans (polysaccharides known as panaxans) and other unidentified compounds has demonstrated hypoglycaemic activity in both normal and alloxan-induced hyperglycaemic mice (Waki et al 1982).

Oral administration of *P. ginseng* root (125.0 mg/kg) three times daily for 3 days reduced hyperglycaemia and improved insulin sensitivity in rats fed a high-fructose chow, suggesting a possible role in delaying or preventing insulin resistance (Liu et al 2005). However, these doses are very high, and human trials need to be conducted to confirm these results.

Diabetic complications

Aqueous extract of ginseng was shown to exert no significant effect on weight in normal rats, while it prevented weight loss in rats with streptozotocin-induced diabetes. Cell proliferation in the dentate gyrus of diabetic rats was increased by ginseng treatment, but it had no effect on cell proliferation in normal rats. These results suggest that ginseng may help reduce the long-term central nervous system complications of diabetes mellitus (Lim et al 2002b).

According to experimental studies, ginseng may also inhibit the formation of glycated haemoglobin due to its antioxidative activity (Bae & Lee 2004).

Steroid receptor activity

Ginseng has been shown to increase the mounting behaviour of male rats and increase sperm counts in rabbit testes. The effect is not by a direct sex

hormone-like function, but probably via a gonadotropin-like action. Ginsenoside Rb1 has been shown to increase luteinising hormone (LH) secretion by acting directly on the anterior pituitary gland in male rats (Tsai et al 2003). Ginsenoside Rh1 failed to activate the glucocorticoid and androgen receptors, but did demonstrate an interaction with oestrogen receptors in vitro. The effect was much weaker than 17-beta-oestradiol. Ginseng is therefore considered to contain phyto-oestrogens (Lee et al 2003). However, there are conflicting reports about oestrogen-binding activity, which may in part be explained by the presence or absence of zearalenone, an oestrogenic mycotoxin contaminant (Gray et al 2004).

OTHER ACTIONS

Prevention of damage from toxins

Ginseng extract has been shown to be beneficial in the prevention and treatment of testicular damage induced by environmental pollutants. Dioxin is one of the most potent toxic environmental pollutants. Exposure to dioxin either in adulthood or during late fetal and early postnatal development causes a variety of adverse effects on the male reproductive system. The chemical decreases spermatogenesis and the ability to conceive and carry a pregnancy to full term. Pretreatment with 100 or 200 mg/kg ginseng aqueous extract intraperitoneally for 28 days prevented toxic effects of dioxin in guinea pigs. There was no loss in body weight, testicular weight or damage to spermatogenesis (Kim 1999). In guinea pigs, *P. ginseng* also improves the survival and quality of sperm exposed dioxin (Hwang et al 2004).

Promoting haemopoiesis

Ginseng is traditionally used to treat anaemia. The total saponin fraction, and specifically Rg1 and Rb1, has been shown to promote haemopoiesis by stimulating proliferation of human granulocyte–macrophage progenitors (Niu et al 2001). The total saponins at a concentration of 50 microgram/mL most effectively promote $CD34^+$ cells to proliferate and differentiate by cooperating with hematopoietic growth factors (Wang et al 2006).

Antioxidant

In-vitro studies did not find various extracts of ginseng to be particularly potent antioxidants against several different free radicals (Kim et al 2002c). However, animal models have demonstrated effects in type 2 diabetes (Ryu et al 2005), particularly for the leaf, which may suppress lipid peroxidation in diabetic rats (Jung et al 2005). Ginseng extract has also been shown to protect muscle from exercise-induced oxidative stress in animal studies (Voces et al 2004).

Whether these effects are directly due to the antioxidant activity of ginseng components or secondary to other mechanisms, such as blood glucose regulation, is unclear. Additionally, ginseng compounds may require in-vivo conversion to active metabolites in order to exert their full effects.

Hair growth

Red ginseng extract (more so than white ginseng), and especially ginsenoside Rb1 and 20(S)-ginsenoside Rg3, has been shown to promote hair growth in mouse hair follicles in vitro (Matsuda et al 2003).

Anti-allergic activity

Ginsenosides have been demonstrated to have anti-allergic activity in vitro. One of the metabolites, 20-*O*-beta-D-glucopyranosyl-20(S)-protopanaxadiol, was found to inhibit beta-hexosaminidase release from rat basophil leukaemia cells and potently reduce passive cutaneous anaphylaxis reaction. The inhibitory activity of protopanaxadiol was more potent than that of disodium cromoglycate, an anti-allergic drug. The compound stabilised membranes but had no effect on hyaluronidase and did not scavenge free radicals. These results suggest that the anti-allergic action of protopanaxadiol originates from its cell membrane-stabilising activity and that the ginsenosides are prodrugs with anti-allergic properties (Choo et al 2003).

Anxiolytic effects

Ginsenosides, and especially ginsenoside Rc, regulate GABA-A receptors in vitro (Choi et al 2003a), and animal models have demonstrated an anxiolytic effect for ginseng saponins (Park et al 2005a).

Wound healing

Ginsenoside Rb2 has been reported to improve wound healing. It is believed that ginsenoside Rb2 enhances epidermal cell proliferation by enhancing the expressions of protein factors related to cell proliferation, such as epidermal growth factor and fibronectin (and their receptors), keratin and collagenase (Choi 2002). Ginsenoside Re may also enhance tissue regeneration by inducing angiogenesis (Huang et al 2005). Topical application of ginseng root extract may also promote collagen production via type I procollagen synthesis, suggesting potential anti-wrinkle effects (Lee 2007).

Improves acne

In an animal model of acne, ginseng extracts reduced the size of comedones by altering keratinisation of the skin and desquamating horny cells in comedones. In a study of experimentally induced hyperkeratosis, ginseng reduced the accumulation of lipids in the epidermis by regulating enzymes associated with epidermal metabolism (Kim et al 1990).

Male fertility

Ginseng-treated rats exhibit a significant increase in sperm count and motility due to activation of cAMP-responsive element modulator in the testes (Park et al 2007).

CLINICAL USE

In the scientific arena, ginseng and the various ginsenosides are used in many forms and administered via various routes. This review will focus primarily on those methods commonly used in clinical practice.

Cancer prevention

The various anticancer actions of *P.ginseng*, as demonstrated in animal and in-vitro trials, support its use as an agent to prevent the development and progression of cancer. A 5-year prospective study of 4634 patients over 40 years of age found that ginseng reduced the relative risk of cancer by nearly 50% (Yun 1996).

A retrospective study of 905 case-controlled pairs taking ginseng showed that ginseng intake reduced the risk of cancer by 44% (odds ratio equal to 0.56). The powdered and extract forms of ginseng were more effective than fresh sliced ginseng, juice or tea. The preventative effect was highly significant ($P < 0.001$). There was a significant decline in cancer occurrence with increasing ginseng intake ($P < 0.05$) (Yun & Choi 1990).

Epidemiological studies in Korea strongly suggest that cultivated Korean ginseng is a non-organ-specific human cancer preventative agent. In case–control studies, odds ratios of cancer of the lip, oral cavity and pharynx, larynx, lung, oesophagus, stomach, liver, pancreas, ovary and colorectum were significantly reduced by ginseng use. The most active compounds are thought to be ginsenosides Rg3, Rg5 and Rh2 (Yun 2003).

Ginseng polysaccharide (18 mg/day) has also been shown to be effective in improving immunological function and quality of life (QOL) in elderly patients with non-small cell lung cancer (Zhang et al 2004).

Chemotherapy

Overexpression of P-glycoprotein or multidrug resistance-associated protein may lead to multidrug resistance of cancer cells. Protopanaxatriol ginsenosides have been shown to sensitise cancer cells to chemotherapeutic agents in vitro by increasing the intracellular accumulation of the drugs through direct interaction with P-glycoprotein (Choi et al 2003b, Kim et al 2003a). The ginsenoside Rh2 possesses strong tumour-inhibiting properties and sensitises multidrug-resistant breast cancer cells to paclitaxel (Jia et al 2004), and animal models demonstrate a synergistic antitumour effect for ginseng acidic polysaccharides and paclitaxel (Shin et al 2004a).

Panax ginseng polysaccharide (12 mg IV daily) has also been trialled during treatment for ovarian cancer, and the authors suggest that it is 'effective, safe and reliable for reducing the toxic effects of chemotherapy' (Fu et al 2005).

In a cohort of 1455 patients with breast cancer recruited to the Shanghai Breast Cancer Study, ginseng use prior to diagnosis was associated with a significantly reduced risk of death (adjusted hazard ratios 0.71; 95% confidence interval: 0.52–0.98). Use of the following diagnosis resulted in a dose-dependent improvement in QOL scores (especially for psychological and social wellbeing) (Cui et al 2006).

Diabetes

The putative effects of Korean ginseng on blood glucose and lipid regulation, oxidative stress and protein glycation suggest a possible role as an adjunctive therapy in the management of diabetes and diabetic complications.

A double-blind, placebo-controlled study with 36 subjects found that 200 mg ginseng elevated mood, improved psychophysical performance, and reduced fasting blood glucose and body weight in patients with newly diagnosed type 2 diabetes (Sotaniemi et al 1995). A double-blind, randomised, dose-finding study reported that 2 g of Korean ginseng rootlets is sufficient to achieve reproducible reductions in postprandial glycaemia (Sievenpiper 2006), although studies using 200–400 mg have also demonstrated benefits for lowering fasting blood glucose levels (Reay et al 2006a).

In a recent clinical trial, 19 participants with well-controlled type 2 diabetes (sex: 11 M:8 F, age: 64 ± 2 years, body mass index (BMI): 28.9 ± 1.4 kg/m^2, HbA_{1c}: 6.5%) received 2 g Korean ginseng 40 minutes prior to meals (total 6 g/day) for 12 weeks in addition to their usual antidiabetic therapy. While HbA_{1c} levels remained unchanged, improvements were noted for plasma glucose (75 g-oral glucose tolerance test-plasma glucose (OGTT-PG) reduced by 8–11%), plasma insulin (PI) (fasting PI and 75 g-OGTT-PI reduced by 33–38%), and insulin sensitivity index (ISI) (75 g-OGTT-ISI increased by 33%) compared with placebo ($P < 0.05$) (Vuksan et al 2008).

Cardiovascular disease

A 2006 systematic review concluded that there is currently a lack of well-designed, randomised, controlled trials to support the use of ginseng to treat cardiovascular risk factors despite some studies suggesting improvements in blood pressure, blood glucose and lipid profiles (Buettner et al 2006).

Although there are reports of ginseng causing hypertension, red ginseng is actually used as an antihypertensive agent in Korea.

Acute administration of an aqueous preparation of Korean ginseng (100 mg/kg body weight) to 12 healthy, nonsmoking male volunteers resulted in an increase in NO levels and a concomitant reduction in mean blood pressure and heart rate (Han et al 2005).

Ginseng is often used in practice as an adjuvant to both conventional and Complementary and Alternative Medicine (CAM) treatments. Trials have reported that 1.5 g three times daily of Korean red ginseng (4.5 g/day) is useful as an adjuvant to antihypertensive medication (Han et al 1995, 1998). It should be noted however that results in these trials while statistically significant (e.g. systolic pressure −5.7 mmHg) may not be clinically significant. A combination of red ginseng and digoxin was found to be more beneficial than either drug alone in an open study of advanced congestive heart failure. There were no adverse reactions (Ding et al 1995). A combination of ginseng and ginkgo extracts has been found to improve circulation and lower blood pressure in a controlled single-dose study of 10 healthy young volunteers (Kiesewetter et al 1992).

Korean red ginseng has also been shown to improve vascular endothelial function in patients with hypertension. The effect is thought to be mediated through increasing the synthesis of nitric oxide (Sung et al 2000).

Hyperlipidaemia

In a small trial of eight males receiving 2 g Panax ginseng extract three times daily (total Panax ginseng extract (PGE) 6 g/day) for 8 weeks, serum total cholesterol, LDL and triglyceride concentrations were decreased by 12, 45 and 24%, respectively, and a 44% increase in HDL was reported (Kim & Park 2003).

Red ginseng, 1.5 g three times daily before meals for 7 days, reduced liver cholesterol, decreased the atherogenic index, and elevated HDL cholesterol in 11 patients (5 normal subjects and 6 with hyperlipidaemia). Serum cholesterol was not significantly altered, but serum triglycerides were significantly decreased (Yamamoto & Kumagai 1982).

Immunomodulation

Ginseng has been shown to significantly enhance NK function in healthy subjects and in those suffering from chronic fatigue syndrome or AIDS ($P < 0.01$) (See et al 1997).

Ginseng polysaccharide injection has been shown, in a randomised study, to improve immunity in 130 patients with nasopharyngeal carcinoma and to reduce adverse reactions to radiotherapy compared with controls (Xie et al 2001).

Red ginseng powder has been shown to restore immunity after chemotherapy and reduce the recurrence of stage III gastric cancer. The 5-year disease-free survival and overall survival rates were significantly higher in patients taking the red ginseng powder during postoperative chemotherapy versus control (68.2 vs 33.3%, 76.4 vs 38.5%, respectively, $P < 0.05$). Despite the limitation of a small number of patients ($n = 42$), these findings suggest that red ginseng powder may help to improve postoperative survival in these patients. Additionally, red ginseng powder may have some immunomodulatory properties associated with CD3 and CD4 activity in patients with advanced gastric cancer during postoperative chemotherapy (Suh et al 2002).

Vaccine adjuvant activity

Ginseng extract (100 mg ginsan G115/day) improved the response to an influenza vaccine in a multicentre, randomised, double-blind, placebo-controlled, two-arm study of 227 subjects. Compared with vaccine without the ginseng, the addition of ginseng resulted in fewer cases of influenza and common cold. Ginseng increased NK activity and increased antibody production (Scaglione et al 1996).

The addition of 2 mg ginseng dry extract per vaccine dose has been shown to potentiate the antibody response of commercial vaccines without altering their safety. The enhancing effect of ginseng was demonstrated during the vaccination of pigs against porcine parvovirus and *Erysipelothrix rhusiopathiae* infections using commercially available vaccines (Rivera et al 2003).

Cognitive function

There is some contention about the benefits of ginseng for improving memory, concentration and learning (Persson et al 2004). Well-controlled clinical trials are lacking, and variations in dosage and standardisation may affect study results.

Some studies have demonstrated that ginseng improves the quality of memory and associated secondary memory (Kennedy et al 2001a). In a randomised, placebo-controlled, double-blind, balanced, crossover study of healthy, young adult volunteers, 400 mg ginseng was shown to improve secondary memory performance on a Cognitive Drug Research computerised assessment battery and two serial subtraction mental arithmetic tasks. Ginseng also improved attention and the speed of performing the memory tasks (Kennedy et al 2002). In a later double-blind, placebo-controlled, balanced, crossover study of 30 healthy young adults, acute administration of ginseng (400 mg) was again shown to improve speed of attention (Sunram-Lea et al 2005).

In a double-blind, placebo-controlled study of healthy young subjects, ginseng extract (G115) improved accuracy and slowed responses during one of two computerised serial subtraction tests (Serial Sevens) and it was also shown to improve mood during these tasks (Kennedy et al 2001b). In acute dosing trials, a single dose of ginseng (200 mg G115 extract, with or without 25 g glucose) and glucose has been shown to enhance cognitive performance in healthy young adults. Participants experienced enhanced performance on a mental arithmetic task and a reduction in subjective feelings of mental fatigue during the later stages of the sustained, cognitively demanding task (Reay et al 2006b).

In a double-blind, randomised, placebo-controlled 8–9-week trial, standardised ginseng extract 400 mg was found to significantly improve abstract thinking ($P < 0.005$) and reaction time (not significant) in 112 healthy subjects over 40 years of age. Ginseng was found not to affect concentration or memory (Sorensen & Sonne 1996).

In a controlled open-label study, 97 consecutive patients with Alzheimer's disease were randomly assigned to a treatment ($n = 58$) or control group ($n = 39$). The treatment group received Korean ginseng powder (4.5 g/day) for 12 weeks, which resulted in improvements in the cognitive subscale of Alzheimer's disease assessment scale (ADAS) and the mini-mental state examination (MMSE) ($P = 0.029$ and $P = 0.009$ vs baseline, respectively). After discontinuing ginseng, the improved ADAS and MMSE scores declined to the levels of the control group (Lee 2008). In addition, similar trials using 0, 4.5 or 9 g ginseng daily found that patients in the high-dose group showed significant improvement on the ADAS and Clinical Dementia Rating after 12 weeks of ginseng therapy ($P = 0.032$ and 0.006, respectively). Improvements in MMSE did not reach statistical significance (Heo et al 2008).

In clinical practice, Korean ginseng and *Ginkgo biloba* are frequently used in combination for cognitive benefits. Combining ginseng with ginkgo dramatically improves memory, concentration and speed of completing mental tasks (Kennedy et al 2001a, Scholey & Kennedy 2002). In clinical trials, ginseng directly modulates cerebroelectrical activity

on EEG recordings to a greater extent than *Ginkgo biloba* (Kennedy et al 2003).

In a double-blind, placebo-controlled study, postmenopausal women aged 51–66 years were randomly assigned to 12 weeks' treatment with a combination formula containing 120 mg *Ginkgo biloba* and 200 mg *Panax ginseng* ($n = 30$) or matched placebo ($n = 27$). The combination appeared to have no effect on mood or cognition after 6 and 12 weeks; however, these doses may be too low (Hartley et al 2004). According to other trials, it would appear that doses of 400–900 mg of ginseng are required for best results and 200 mg doses have been associated with 'cognitive costs', slowing performance on attention tasks (Kennedy & Scholey 2003).

Menopausal symptoms

Korean red ginseng is used to alleviate symptoms associated with menopause; 6 g ginseng for 30 days was shown in a small study of 20 women significantly ($P < 0.001$) to improve menopausal symptoms, in particular fatigue, insomnia and depression. The women treated had a significant decrease in cortisol and cortisol-to-dehydroepiandrosterone ratio ($P < 0.05$). No adverse effects were recorded (Tode et al 1999).

Erectile dysfunction

Korean red ginseng has been shown to alleviate erectile dysfunction and improve the ability to achieve and maintain erections even in patients with severe erectile dysfunction (Price & Gazewood 2003). Ginsenosides can facilitate penile erection by directly inducing the vasodilatation and relaxation of the penile corpus cavernosum. Moreover, the effects of ginseng on the corpus cavernosum appear to be mediated by the release and/or modification of release of NO from endothelial cells and perivascular nerves (Murphy & Lee 2002). In men with type 2 diabetes, oxidative stress has been suggested as a contributing factor to erectile dysfunction and animal studies suggest that ginseng can preserve 'potency' via its antioxidant effect (Ryu et al 2005).

In a double-blind, placebo-controlled study, 60 patients presenting with mild or mild to moderate erectile dysfunction received 1 g (three times daily) of Korean ginseng or placebo. In the five-item International Index of Erectile Function (IIEF)-5, 66.6% (20 patients) reported improved erection, rigidity, penetration and maintenance ($P < 0.01$) after 12 weeks. Serum testosterone, prolactin and cholesterol were not significantly different (de Andrade et al 2007).

In a double-blind crossover study, 900 mg Korean red ginseng was found to significantly improve the Mean IIEF scores compared with placebo. Significant subjective improvements in penetration and maintenance were reported by participants, and penile tip rigidity on the RigiScan showed significant improvement for ginseng versus placebo (Hong et al 2002).

A significant improvement in erectile function, sexual desire and intercourse satisfaction was demonstrated in 45 subjects following 8 weeks' oral administration of Korean red ginseng (900 mg three times daily) in a double-blind, placebo-controlled, crossover trial. Subjects demonstrated significant improvement in mean IIEF scores compared with placebo (baseline, 28 ± 16.7; Korean red ginseng, 38.1 ± 16.6; placebo, 30.9 ± 15.7) (Hong et al 2003).

Quality of life

An 8-week, randomised, double-blind study found that 200 mg/day ginseng ($n = 15$, placebo: $n = 15$) improved aspects of mental health and social functioning after 4 weeks' therapy but that these differences disappeared with continued use (Ellis & Reddy 2002). A review of eight clinical studies with ginseng found some improvement in QOL scores. However, the findings were equivocal. Despite some positive results, improvement in overall health-related QOL cannot, given the current research, be attributed to *P. ginseng*. However, the possibility that various facets of QOL may have improved and the potential of early transient effects cannot be discounted (Coleman et al 2003). A double-blind, placebo-controlled, randomised clinical trial of 83 subjects also did not find ginseng to enhance psychological wellbeing in healthy young adults (Cardinal & Engels 2001).

A double-blind, placebo-controlled, crossover study found that 1200 mg ginseng was only slightly more effective than placebo and not as effective as a good night's sleep in improving bodily feelings, mood and fatigue in 12 fatigued night nurses. Volunteers slept less and experienced less fatigue but rated sleep quality worse after ginseng administration (Hallstrom et al 1982).

A recent double-blind, placebo-controlled, balanced, crossover design of 30 healthy young adults taking *P. ginseng* extract (200 or 400 mg) or placebo demonstrated improvements in performance and subjective feelings of mental fatigue during sustained mental activity. It has been hypothesised that this effect may be due in part to the ability of ginseng to regulate blood glucose levels (Reay et al 2005).

Adaptogenic and tonic effects

A randomised double-blind study involving 232 subjects between the ages of 25 and 60 years found that extract equivalent to about 400 mg ginseng root for 4 weeks significantly improved fatigue. Side effects were uncommon, with only two subjects withdrawing from the study (Le Gal & Cathebras 1996).

A randomised double-blind study of 83 subjects found that extract equivalent to 1 g ginseng root for 4 months decreased the risk of contracting a common cold or bronchitis and improved appetite, sleep, wellbeing and physical performance (Gianoli & Riebenfeld 1984).

Improved athletic performance

Ginseng is used by many athletes to improve stamina and to facilitate rapid recovery from injuries; however, supporting evidence from well-designed clinical trials is lacking. To examine the

effects of ginseng supplements on hormonal status following acute resistance exercise, eight male college students were randomly given water (control group) or 20 g ginseng root extract treatment immediately after a standardised training exercise. Human growth hormone, testosterone, cortisol and insulin-like growth factor 1 levels were determined by radioimmunoassay. The responses of plasma hormones following ginseng consumption were not significant between the control and the ginseng groups during the 2-hour recovery period (Youl et al 2002).

Although ginseng is commonly used to improve endurance, a double-blind study of 19 healthy active women found that 400 mg of a ginseng extract (G115) did not improve supramaximal exercise performance or short-term recovery. Analysis of variance using pretest to posttest change scores revealed no significant difference between the ginseng and placebo study groups for the following variables measured: peak anaerobic power output, mean anaerobic power output, rate of fatigue and immediate postexercise recovery heart rates (Engels et al 2001). A recent study by the same authors also failed to find any benefit from ginseng (400 mg/day G115; equivalent to 2 g *P. ginseng* C.A. Meyer root material for 8 weeks) on improving physical performance and heart rate recovery of individuals undergoing repeated bouts of exhausting exercise (Engels et al 2003). When 60 men from the Naval Medical Corps, Royal Thai Navy (aged 17–22 years), given 3 g/day of ginseng or placebo for an 8-week period, were measured for blood lactic acid levels for determination of lactate threshold (LT), no improvements were noted, nor was there any beneficial effect on physical performance (Kulaputana et al 2007).

A small study of seven healthy male subjects given 2 g ginseng (three times daily) for 8 weeks reported a significant increase in exercise duration until exhaustion (+1.5 min; $P < 0.05$), which was related to improvements in lipid peroxidation and scavenger enzymes (Kim et al 2005); however, this study is too small to make generalisations.

OTHER USES

Gastroprotection during heart surgery

In a trial of 24 children undergoing heart surgery for congenital heart defects, 12 children received 1.35 mg/kg ginsenoside compound or placebo intravenously before and throughout the course of cardiopulmonary bypass surgery. Ginseng administration resulted in attenuation of gastrointestinal injury and inflammation (Xia et al 2005).

Respiratory disease

Ginseng extract (G115) has been shown significantly ($P < 0.05$) to improve pulmonary function test, maximum voluntary ventilation, maximum inspiratory pressure and maximal oxygen consumption (VO_{2max}) in a study of 92 patients suffering moderately severe chronic obstructive pulmonary disease ($n = 49$, G115 100 mg twice daily for 3 months) (Gross et al 2002).

Helicobacter pylori

Helicobacter pylori can provoke gastric inflammation, ulceration and DNA damage, resulting in an increased risk of carcinogenesis (Park et al 2005b). As preliminary evidence suggests that *P. ginseng* inhibits the growth of *H. pylori* (Kim et al 2003b) and can inhibit adhesion (Lee et al 2004b), it may be useful as a gastroprotective agent against *H. pylori*-associated gastric mucosal cell damage (Park 2005b).

HIV infection

Long-term intake of Korean ginseng slows the depletion of $CD4^+$ T cells and may delay disease progression in people with HIV type 1 (Sung et al 2005). Ginseng intake in HIV-1-infected patients may also be associated with the occurrence of grossly deleted nef genes (gDeltanef) (Cho et al 2006) and gross deletions (gDelta) in HIV-1 5' LTR and gag regions (Cho & Jung 2008). Long-term intake (60 ± 15 months) has also been shown to delay the development of resistance mutation to zidovudine (Cho et al 2001).

DOSAGE RANGE

- Extract equivalent to 0.9–3 g crude ginseng root (Bensky & Gamble 1986).
- Standardised extract: 1.5–4.0% total ginsenosides calculated as ginsenoside Rg1.
- Liquid extract (1:2): 1–6 mL/day.
- Cognitive function: Clinical trials using 1.5–3 g three times daily have reported benefits. Lower doses may be associated with 'cognitive costs' and slowing performance on attention tasks (Kennedy & Scholey 2003).
- Cardiovascular use: 1.5–2 g three times daily.

Many of the clinical studies published in the scientific literature have used a proprietary extract of ginseng standardised to 4% total ginsenosides (G115 or Ginsana produced by Pharmaton, Lugano, Switzerland).

Ginseng is usually given in the earlier part of the day. It should not be given in the evening, unless it is used to promote wakefulness. Ginseng is usually not given to children.

ADVERSE REACTIONS

Ginseng abuse syndrome (hypertension, nervousness, insomnia, morning diarrhoea, inability to concentrate and skin reactions) has been reported, and there has been a report of a 28-year-old woman who had a severe headache after ingesting a large quantity of ethanol-extracted ginseng. Cerebral angiograms showed 'beading' appearance in the anterior and posterior cerebral and superior cerebellar arteries, consistent with cerebral arteritis (Ryu & Chien 1995). High doses (15 g/day) have been associated with confusion, depression and depersonalisation in four patients (Coon & Ernst 2002).

However, the majority of the scientific data suggest that ginseng is rarely associated with adverse events or drug interactions. A systematic review found that the most commonly experienced adverse events are headache, sleep and gastrointestinal disorders. Data from clinical trials suggest that the

incidence of adverse events with ginseng monopreparations is similar to that of placebo. Any documented effects are usually mild and transient. Combined preparations are more often associated with adverse events, but causal attribution is usually not possible (Coon & Ernst 2002).

Allergic reactions to Korean ginseng, including occupation asthma, may occur via an IgE-mediated mechanism (Kim 2008). A case of suspected ginseng allergy has recently been reported in the scientific literature. The case involved a 20-year-old male who developed urticaria, dyspnoea and hypotension after ingesting ginseng syrup. The subject recovered fully and was discharged after 24 h (Wiwanitkit & Taungjararuwinai 2004).

While ginseng use has been associated with the development of hypertension, it has actually been shown to reduce blood pressure in several studies (Coon & Ernst 2002).

Ginseng has very low toxicity. Subacute doses of 1.5–15 mg/kg of a 5:1 ginseng extract did not produce negative effect on body weight, food consumption, haematological or biochemical parameters or histological findings in dogs (Hess et al 1983), and no effects have been observed from the administration of similar doses in two generations of rat offspring (Hess et al 1982).

Traditionally, ginseng is not recommended with other stimulants such as caffeine and nicotine, and a case report exists of a 39-year-old female experiencing menometrorrhagia, arrhythmia and tachycardia after using oral and topical ginseng along with coffee and cigarettes (Kabalak et al 2004).

SIGNIFICANT INTERACTIONS

Albendazole

Panax ginseng significantly accelerated the intestinal clearance of the anthelmintic albendazole sulfoxide, when coadministered to rats (Merino et al 2003).

Alcohol

Ginseng may increase the clearance of alcohol from the blood according to an open trial of 14 healthy volunteers (Coon & Ernst 2002) — beneficial interaction possible, but needs confirmation.

Chemotherapy, radiotherapy and general anaesthetics

Preliminary evidence suggests that *P.ginseng* saponins may reduce nausea and vomiting associated with chemotherapy, radiotherapy and general anaesthetics by antagonising serotonin (5-hydroxytryptamine) type 3A receptors (Min et al 2003). Ginseng may also help to sensitise cancer cells to chemotherapeutic agents according to preliminary evidence.

Digoxin

Ginseng contains glycosides with structural similarities to digoxin, which may modestly interfere with digoxin results (Dasgupta et al 2003). These naturally occurring glycosides may cause false elevation of fluorescence polarisation and falsely low microparticle enzyme results, although Tina-quant results appear unaffected (Dasgupta & Reyes 2005). It should be noted that measuring free digoxin does not eliminate these modest interferences in serum digoxin measurement by the Digoxin III assay (Dasgupta et al 2008). There are no confirmed case reports of actual interaction (Chow et al 2003, Dasgupta et al 2003).

Drugs metabolised chiefly by CYP1A, CYP2D6 and CYP3A4

Mixed reports exist as to whether ginseng may act as an inhibitor of cytochrome CYP1A (Gurley et al 2005, Lee et al 2002b, Yu et al 2005) or CYP2D6 (Gurley et al 2005). Ginsenosides F1 and Rh1 (but not ginseng extract) may inhibit CYP3A4 at 10 micromolar (Etheridge et al 2007). Whether these effects are likely to be clinically significant has not been established. Observe for increased drug bioavailability and clinical effects.

Nifedipine

Ginseng increased the mean plasma concentration of the calcium channel blocker nifedipine by 53% at 30 minutes in an open trial of 22 healthy subjects. Effects at other time points were not reported (Smith et al 2001).

Vancomycin

In animal studies, the combination of ginseng polysaccharides with vancomycin resulted in a 100% survival rate for animals treated for *Staphylococcus aureus* compared to only 67 or 50% survival in animals treated with ginseng polysaccharides or vancomycin alone (Lim et al 2002b). A beneficial additive effect is possible, but clinical use in humans has not yet been established.

Warfarin

No effects on the pharmacokinetics or pharmacodynamics of either S-warfarin or R-warfarin were revealed in an open-label, crossover randomised trial of 12 healthy male subjects who received a single 25-mg dose of warfarin alone or after 7 days' pretreatment with ginseng (Jiang et al 2004). Whether these effects are consistent in less 'healthy' people likely to be taking warfarin or for prolonged concurrent use is unclear.

There have been two case reports of ginseng reducing the antithrombotic effects of warfarin (Janetzky & Morreale 1997, Rosado 2003). Additionally, it inhibits platelet aggregation according to both in vitro and animal studies. Avoid using this combination unless under medical supervision to monitor antithrombotic effects.

Zidovudine

Long-term intake (60 ± 15 months) of Korean red ginseng in HIV-1-infected patients has been shown to delay the development of resistance mutation to zidovudine (Cho et al 2001).

CONTRAINDICATIONS AND PRECAUTIONS

Korean ginseng is generally contraindicated in acute infections with fever and in persons who are very hot, tense and overly stimulated. Overuse may result in headache, insomnia and palpitation (Bensky & Gamble 1986). Ginseng should not be

PRACTICE POINTS/PATIENT COUNSELLING

Traditional use

Ginseng is traditionally used for deficiency of Qi (energy/life force) manifested by shallow respiration, shortness of breath, cold limbs, profuse sweating and a weak pulse (such as may occur from severe blood loss). Ginseng is also used for wheezing, lethargy, lack of appetite, abdominal distension and chronic diarrhoea. Ginseng may also be used for palpitations, anxiety, insomnia, forgetfulness and restlessness associated with low energy and anaemia (Bensky & Gamble 1986)

Scientific evidence

There is some scientific evidence for the beneficial effects of ginseng for the following conditions. In practice, it is mostly used as a supportive treatment and combined with other herbs to treat a specific condition.

- Prevention and supportive treatment of cancer
- Chronic immune deficiency
- Menopausal symptoms
- Erectile dysfunction
- Chronic respiratory disease
- Enhancement of psychomotor activity, memory and concentration
- Adaptogenic effects in any chronic condition and for the elderly and infirm
- Type 1 diabetes
- Cardiovascular disease (the effects on hypertension remain to be fully investigated)
- QOL (equivocal scientific support)

Commission E recommends ginseng as a tonic for invigoration and fortification in times of fatigue, debility and convalescence or declining capacity for work and concentration. The World Health Organization suggests that ginseng can be used as a prophylactic and restorative agent for enhancement of mental and physical capacities, in cases of weakness, exhaustion, tiredness and loss of concentration and during convalescence (Blumenthal 2001).

taken concurrently with other stimulants including caffeine and should be discontinued 1 week before major surgery. Use in hypertension should be supervised; however, it may prove beneficial for this indication.

PREGNANCY USE

Ginseng is traditionally used in Korea as a tonic during pregnancy. Commission E does not list any restrictions (Blumenthal 2001). There is in-vitro evidence of teratogenicity based on exposure to isolated ginsenosides (especially Rb1) (Chan et al 2003) at much higher levels than achievable through normal consumption in humans and conflicting evidence as to its oestrogenic properties. In light of the lack of good clinical evidence, Korean ginseng should be used cautiously during pregnancy (especially the first trimester) and lactation until more data are available (Seely et al 2008).

In a two-generation rat study, a ginseng extract fed at doses as high as 15 mg/kg/day did not produce adverse effects on reproductive performance, including embryo development and lactation (Hess et al 1982).

PATIENTS' FAQs

What will this herb do for me?

Ginseng is a safe herb used to support the body during times of prolonged stress or chronic disease and to restore mental and physical functioning during the rehabilitative process. Numerous studies have identified a range of pharmacological activities that suggest that it may be useful in the treatment of many conditions.

When will it start to work?

In practice, it generally appears that ginseng has a quick onset of action with the condition continuing to improve with long-term use; however, this will vary depending on the individual and the indication.

Are there any safety issues?

Ginseng may interact with warfarin and other blood-thinning drugs and should not be used with these medications, unless under medical supervision. Avoid use in children or in hypertension, unless under supervision. Use with caution in pregnancy.

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Ginseng — Siberian

HISTORICAL NOTE Siberian ginseng has been used for over 2000 years, according to Chinese medical records, where it is referred to as Ci Wu Jia. It was used to prevent colds and flu and to increase vitality and energy. In modern times, it has been used by Russian cosmonauts for improving alertness and energy and to aid in adaptation to the stresses of life in space. It also has been used as an ergogenic aid by Russian athletes before international competitions (Mills & Bone 2000) and used after the Chernobyl accident to counteract the effects of radiation (Chevallier 1996).

OTHER NAMES
Ci Wu Jia, devil's bush, devil's shrub, eleuthero, eleutherococcus, eleuthero root, gokahi, ogap'I, russisk rod, taigawurzel, touch-me-not, Wu Jia Pi

BOTANICAL NAME/FAMILY
Eleutherococcus senticosus (synonym: *Acanthopanax senticosus*) (family Araliaceae)

PLANT PART USED
Root, rhizome

CHEMICAL COMPONENTS
Glycosides (eleutherosides A–M, including saponins, coumarins, lignans, phenylpropanoids, oleanolic acids, triterpenes, betulinic acid and vitamins), steroid glycoside (eleutheroside A), lignans (syringin, sesamin, chlorigenic acid), glycans (eleutherans A–G), triterpenoid saponins (friedelin), saponin (protoprimulagenin A), hydroxycoumarin (isofraxidin), phenolics, polysaccharides, lignans, coumarins and resin.

Nutrients include magnesium 723 microgram/g, aluminium 188 microgram/g and manganese 37 microgram/g and vitamins A and E (Eleutherococcus senticosus 2006, Meacham et al 2002, Nissen 2003, Skidmore-Roth 2001, Panossian et al 1999).

MAIN ACTIONS

Adaptogenic (modulates stress response)
Siberian ginseng appears to alter the levels of different neurotransmitters and hormones involved in the stress response, chiefly at the hypothalamic-pituitary-adrenal axis (HPA) axis. Various mechanisms have been proposed including inhibition of catechol-O-methyltransferase, which inactivates catecholamines (Gaffney et al 2001a). As a result, catecholamine levels are not depleted and release of new catecholamines from nerve synapses is decreased (Panossian et al 1999). In theory, this may reduce the risk of the organisms' adaptive responses becoming depleted and moving into the exhaustion phase of the stress response. In addition, eleutherosides have been shown to improve carbohydrate metabolism and energy provision and increase the synthesis of protein and nucleic acids, although the direct molecular targets responsible for this adaptive response remain unknown (Panossian et al 1999). Eleutherosides have also been reported to bind to receptor sites for progestin, oestrogen, mineralocorticoids and glucocorticoids in vitro and therefore may theoretically exert numerous pharmacological actions important for the body's stress response (Pearce et al 1982).

Owing to such actions, herbalists and naturopaths describe the herb's overall action as 'adaptogenic'. The term 'adaptogen' describes substances that increase the ability of an organism to adapt to environmental factors and to avoid damage from such factors (Panossian et al 1999). The term 'allostasis' (see Clinical note) has been adopted in the medical arena to describe 'the ability to achieve stability through change'.

Clinical note — Allostasis
Allostasis is the body's adaptation to stress. Allostatic (adaptive) systems are critical to survival and enable us to respond to changes in our physical (such as asleep, awake, standing, sitting, eating, exercising and infection) and psychological states (such as anticipation, fear, isolation, worry and lack of control). The consumption of tobacco, alcohol and our dietary choices also induces allostatic responses (McEwan 1998). These systems are complex and have broad boundaries, in contrast to the body's homeostatic systems (e.g. blood pH and body temperature), which are maintained within a narrow range.

Most commonly, allostatic responses involve the sympathetic nervous system and the HPA axis. Upon activation (e.g. when a challenge is perceived), catecholamines are released from nerves and the adrenal medulla, corticotrophin is secreted from the pituitary and cortisol is released from the adrenal cortex. Once the threat has passed (e.g. the environment is more comfortable or infection is controlled), the system is inactivated and levels of cortisol and catecholamine secretion return to baseline.

Chronic exposure to stress can lead to allostatic load, a situation resulting from chronic overactivity or underactivity of allostatic systems. The situation is characterised by maladaptive responses whereby systems become inefficient or do not turn off appropriately. Currently, there is much interest in understanding the association between numerous diseases such as cardiovascular disease and overwhelming allostatic load.

One measure that is used to gauge an individual's allostatic response is the cortisol response to a variety of stressors. As such, cortisol is seen as the classical 'stress' hormone.

Although the mechanism of action responsible is still unclear, several theories have been proposed to explain the effect of Siberian ginseng on allostatic systems, largely based on the pharmacological actions observed in test tube and animal studies. Depending on the stage of the stress response, Siberian ginseng can act in different ways to support the 'stress system'. Research suggests that there is a threshold of stress below which the herb increases the stress response and above which it decreases the stress response (Gaffney et al 2001b). Therefore, for example, if allostatic load is such that responses have become inadequate, then the resulting increase in hormone levels would theoretically induce a more efficient response. Alternatively, situations of chronic overactivity, also due to allostatic load, would respond to Siberian ginseng in a different way, with negative feedback systems being triggered to inactivate the stress response (Gaffney et al 2001a). As a result, Siberian ginseng could theoretically induce quite different effects, largely dependent on whether allostatic responses were underactive or overwhelmed.

The dosing regimen may also be significant. While multi-dose administration in chronic stress engages the HPA axis balancing the switch-on and switch-off responses, single doses (~ 4 mL) in acute stress trigger a rapid response from the sympathoadrenal system, resulting in secretion of catecholamines, neuropeptides, adenosine triphosphate (ATP) and nitric oxide (Panossian & Wagner 2005). Studies have demonstrated that maximal effects are achieved around 4 weeks but do not persist at the 8-week time point, which may help to explain the practice of giving Siberian ginseng for 6 weeks with a 2-week break before repeating.

Immunomodulation

Siberian ginseng appears to exert an immunomodulatory rather than just an immunosuppressive or stimulating action; however, evidence for the immune enhancing effects of Siberian ginseng is contradictory. Clinical studies in vitro and in vivo have revealed stimulation of general non-specific resistance and an influence on T-lymphocytes, natural killer (NK) cells and cytokines (Bohn et al 1987, Schmolz et al 2001), although other studies suggest that Siberian ginseng does not significantly stimulate the innate macrophage immune functions that influence cellular immune responses (Wang et al 2003). Alternatively, another in-vitro study has demonstrated that activation of macrophages and NK cells does occur and may be responsible for inhibiting tumour metastasis both prophylactically and therapeutically (Yoon et al 2004).

The main constituents responsible appear to be lignans (sesamin, syringin) and polysaccharides, such as glycans, which demonstrate immunostimulant effects in vitro (Davydov & Krikorian 2000, Wagner et al 1984). Additionally, effects on the HPA axis will influence immune responses.

It has been suggested that eleutheroside E may be responsible for the improved recovery from reduced NK activity and the inhibition of corticosterone elevation induced by forced swimming in mice (Kimura & Sumiyoshi 2004) and may contribute to the antifatigue action.

Antiviral

In vitro studies show a strong antiviral action, inhibiting the replication of ribonucleic acid (RNA) type viruses such as human rhinovirus, respiratory syncytial virus and influenza A virus (Glatthaar-Saalmuller et al 2001).

Anabolic activity

Syringin and other eleutherosides appear to improve carbohydrate metabolism and energy provision by increasing the formation of glucose-6-phosphate and activating glucogen transport (Panossian et al 1999), and Siberian ginseng extracts have been reported to improve the metabolism of lactic and pyruvic acids (Farnsworth et al 1985). Additionally, preliminary evidence of possible anabolic effects makes this herb a popular treatment among athletes in the belief that endurance, performance and power may improve with its use.

While initial animal studies showed promise for improving weight gain and increasing organ and muscle weight (Farnsworth et al 1985, Kaemmerer & Fink 1980), clinical studies confirming whether anabolic effects occur also in humans could not be located.

OTHER ACTIONS

Anticoagulant and antiplatelet effects

Animal studies have demonstrated prevention against thrombosis induced by immobilisation (Shakhmatov et al 2007), and the 3,4-dihydroxybenzoic acid constituent of Siberian ginseng has demonstrated antiplatelet activity in vivo (Yun-Choi et al 1987). A controlled trial using Siberian ginseng tincture for 20 days in 20 athletes detected a decrease in the blood coagulation potential and activity of the blood coagulation factors that are normally induced by intensive training of the athletes (Azizov 1997). Whether the effects also occur in non-athletes is unknown.

Vascular relaxant

In vitro studies have demonstrated vasorelaxant effects for Siberian ginseng. The effect is thought to be endothelium dependent and mediated by NO and/or endothelium-derived hyperpolarising factor, depending on the size of the blood vessel. Other vasorelaxation pathways may also be involved (Kwan et al 2004).

Anti-allergic

In-vitro studies demonstrate that Siberian ginseng has anti-allergic properties in mast cell-mediated allergic reactions (Jeong et al 2001). The mechanism appears to involve inhibition of histamine, tumour necrosis factor-alpha (TNF-alpha) and interleukin-6.

Anti-inflammatory

Excess production of nitric oxide (NO) is a characteristic of inflammation, and Siberian ginseng has been shown to significantly suppress NO production and inducible nitric oxide synthase (iNOS) gene expression in a dose-dependent manner (Lin et al 2008). The downregulation of iNOS expression may be the result of inhibition of intracellular peroxide production (Lin et al 2008) or through blocking c-Jun NH2-terminal kinase (JNK) and Akt activation (Jung et al 2007). Contradictory results have been shown for inhibition of cyclooxygenase (COX)-2 expression (Jung et al 2007, Raman et al 2008).

Radioprotective

Animal studies have found that administration of Siberian ginseng prior to a lethal dose of radiation produced an 80% survival rate in mice (Miyanomae & Frindel 1988). This result suggests that Siberian ginseng may protect against radiation toxicity.

Cardioprotective

Oral administration of Siberian ginseng (1 mL/kg) to rats for 8 days prevented stress-induced heart damage and chronic administration increased beta-endorphin levels and improved cardiac tolerance to D, L-isoproterenol and arrhythmia caused by

adrenaline. The cardioprotective and antiarrhythmic effect may be related to an increase in endogenous opioid peptide levels (Maslov & Guzarova 2007). Benefits following a 45-min coronary artery occlusion were not demonstrated in this study (Maslov & Guzarova 2007) but have been in studies using Siberian ginseng in a polypharmacy combination known as 'Tonizid'® (Lishmanov et al 2008).

Neuroprotective

Preliminary animal studies have suggested possible neuroprotective effects in transient middle cerebral artery occlusion in Sprague-Dawley rats. Infarct volume was reduced by 36.6% by inhibiting inflammation and microglial activation in brain ischaemia after intraperitoneal injection of a water extract of Siberian ginseng (Bu et al 2005). Similarly, intraperitoneal injection of Siberian ginseng was found to relieve damage to neurons following hippocampal ischaemia hypoxia and improve the learning and memory of rats with experimentally induced vascular dementia (Ge et al 2004). Siberian ginseng extract appears to protect against neuritic atrophy and cell death under amyloid beta treatment; the effect is thought to be due at least in part to eleutheroside B (Tohda et al 2008). The saponins present in Siberian ginseng have also been shown to protect against cortical neuron injury induced by anoxia/reoxygenation by inhibiting the release of NO and neuron apoptosis in vitro (Chen et al 2004).

Hepatoprotective

Animal studies have demonstrated that an intravenous extract of Siberian ginseng decreased thioacetamide-induced liver toxicity when given before and after thioacetamide administration (Shen et al 1991). More recently, oral administration of aqueous extract and polysaccharide was found to attenuate fulminant hepatic failure induced by D-galactosamine/lipopolysaccharide in mice, reducing serum aspartate aminotransferase (AST), alanineaminotransferase (ALT) and tissue necrosis factor (TNF)-alpha levels (Park et al 2004). The protective effect is thought to be due to the water-soluble polysaccharides. Coadministration of Siberian ginseng may also act to enhance the antihypoxant action of amtizole, improving the protective effect on hepatic antitoxic function and lipid metabolism (Kushnerova & Rakhmanin Iu 2008).

Reduces obesity

Animal studies have demonstrated that the inclusion of Siberian ginseng attenuated the 'weight gain, serum low density lipoprotein (LDL) cholesterol concentration and liver triglyceride accumulation in mice with obesity induced by high-fat diets' (Cha et al 2004).

Glycaemic control and insulin-sensitising effect

Animal studies have indicated a potential for hypoglycaemic effects when used intravenously. Syringin appears to enhance glucose utilisation (Niu et al 2008) and lower plasma glucose levels in animal experiments. The effect may be due to an increase in the release of acetylcholine from nerve terminals, stimulating muscarinic M (3) receptors in pancreatic cells to increase insulin release (Liu et al 2008). Syringin may also enhance the secretion of beta-endorphin from the adrenal medulla to stimulate peripheral micro-opioid receptors, resulting in a decrease of plasma glucose in insulin-depleted diabetic rats (Niu et al 2007).

Eleutherans A–G exert marked hypoglycaemic effects in normal and alloxan-induced hyperglycaemic mice (Hikino et al 1986), and eleutherosides show an insulin-like action in diabetic rats (Dardymov et al 1978). However, these effects have not been borne out in human studies (Farnsworth et al 1985) and may not relate to oral dosages of Siberian ginseng.

A small, double-blind, randomised, multiple, crossover study using 12 healthy participants actually showed an increase in postprandial plasma glucose at 90 and 120 min when 3 g Siberian ginseng was given orally 40 min before a 75-g oral glucose tolerance test (Sievenpiper et al 2004). More recently, oral administration of an aqueous extract of Siberian ginseng was shown to improve insulin sensitivity and delay the development of insulin resistance in rats (Liu et al 2005). As a result, further trials in people with impaired glucose tolerance and/or insulin resistance are warranted.

CLINICAL USE

Stress

Siberian ginseng is widely used to treat individuals with nervous exhaustion or anxiety due to chronic exposure to stress or what is now termed 'allostatic load situations'. The biochemical effects on stress responses observed in experimental and human studies provide a theoretical basis for this indication (Abramova et al 1972, Gaffney et al 2001a).

One placebo-controlled study conducted over 6 weeks investigated the effects of an ethanolic extract of Siberian ginseng (8 mL/day, equivalent to 4 g/day dried root). In the study, active treatment resulted in increased cortisol levels, which may be consistent with animal research, suggesting a threshold of stress below which Siberian ginseng increases the stress response and above which it decreases the stress response (Gaffney et al 2001b).

Fatigue

Siberian ginseng is used to improve physical and mental responses during convalescence or fatigue states. While traditional stimulants can produce a temporary increase in work capacity followed by a period of marked decrease, the initial increase in performance from adaptogens is followed by only a slight dip and performance remains above basal levels (Panossian et al 1999). The ability of Siberian ginseng to increase levels of noradrenaline, serotonin, adrenaline and cortisol provides a theoretical basis for its use in situations of fatigue. However, controlled studies are limited.

A randomised, double-blind, placebo-controlled trial of 300 mg/day (*E. senticosus* dry extract) for 8 weeks assessed health-related quality of life scores in 20 elderly people. Improvements were observed

in social functioning after 4 weeks of therapy but did not persist to the 8-week time point. It would appear that improvements diminish with continued use (Cicero et al 2004), which may help to explain the practice of giving Siberian ginseng for 6 weeks with a 2-week break before repeating.

A recent randomised placebo-controlled trial evaluated the effectiveness of Siberian ginseng in chronic fatigue syndrome (CFS). No significant improvements were demonstrated overall; however, subgroup analysis showed improvements in fatigue severity and duration ($P < 0.05$), in CFS sufferers with less severe fatigue at 2-month follow-up (Hartz et al 2004). Further studies are required to determine whether Siberian ginseng may be a useful therapeutic option in cases of mild to moderate fatigue.

Commission E approves the use of Siberian ginseng as a tonic in times of fatigue and debility, for declining capacity for work or concentration and during convalescence (Blumenthal et al 2000). In practice, it is often used in low doses in cases of fatigue due to chronic stress (Gaffney et al 2001a).

Ergogenic aid

Siberian ginseng extracts have been reported to provide better usage of glycogen and high-energy phosphorus compounds and improve the metabolism of lactic and pyruvic acids (Farnsworth et al 1985). Experimental data suggest that syringin and other eleutherosides may improve carbohydrate metabolism and energy provision by increasing the formation of glucose-6-phosphate and activating glucogen transport (Panossian et al 1999). While initial animal studies showed promise for improving weight gain and increasing organ and muscle weight (Wagner et al 1985), recent randomised, controlled clinical trials have produced inconsistent results in healthy individuals and athletes (Dowling et al 1996, Eschbach et al 2000, Mahady et al 2000), and a recent review concluded that only poorer quality trials have demonstrated benefit while well-designed trials have not shown significant improvement in endurance performance, cardiorespiratory fitness or fat metabolism during exercise ranging in duration from 6 to 120 minutes (Goulet & Dionne 2005).

In the mid 1980s, a Japanese controlled study conducted on six male athletes over 8 days showed that Siberian ginseng extract (2 mL twice daily) improved work capacity compared with a placebo (23.3 versus 7.5%) in male athletes, owing to increased oxygen uptake ($P < 0.01$). Time to exhaustion (stamina) also increased (16.3 versus 5.4%, $P < 0.005$) (Asano et al 1986). Other research however has failed to confirm these effects (Dowling et al 1996, Eschbach et al 2000).

A randomised, double-blind, crossover trial using a lower dose of 1200 mg/day Siberian ginseng for 7 days reported that treatment did not alter steady-state substrate use or 10 km cycling performance time (Eschbach et al 2000). Additionally, an 8-week, double-blind, placebo-controlled study involving 20 experienced distance runners failed to detect significant changes to heart rate, oxygen consumption, expired minute volume, respiratory exchange ratio, perceived exertion or serum lactate levels compared with placebo. Overall, both submaximal and maximal exercise performance were unchanged (Dowling et al 1996).

Siberian ginseng may however reduce blood coagulation factors induced by intensive training in athletes (Azizov 1997) and has been shown in combination with micronutrients to improve iron metabolism and immunological responsiveness in 39 high-grade unarmed self-defence sportsmen (Nasolodin et al 2006). Whether these effects also occur in other scenarios is yet to be established.

Clinical studies investigating whether ergogenic or anabolic effects observed in experimental studies occur in humans are lacking, and therefore Siberian ginseng cannot currently be recommended to improve athletic performance (Palisin & Stacy 2006). Siberian ginseng does not appear on 'The 2008 Prohibited List' of the World Anti-doping Agency (WADA 2008).

Prevention of infection

Due to the herb's ability to directly and indirectly modulate immune responses, it is also used to increase resistance to infection. One double-blind study of 1000 Siberian factory workers supports this, reporting a 50% reduction in general illness and a 40% reduction in absenteeism over a 12-month period, following 30 days' administration of Siberian ginseng (Farnsworth et al 1985).

More recently, a 6-month controlled trial in males and females with recurrent herpes infection found that Siberian ginseng (2 g/day) successfully reduced the frequency of infection by 50% (Williams 1995).

In practice, Siberian ginseng is generally used as a preventative medicine, as administration during acute infections is widely thought to increase the severity of the illness, although this has not been borne out in controlled studies using Siberian ginseng in combination with other herbs. A small randomised controlled trial (RCT) demonstrated a significant reduction in the severity of familial Mediterranean fever in children using a combination of Siberian ginseng with licorice, andrographis and schisandra (Amaryan et al 2003), and a combination of Siberian ginseng with schisandra and rhodiola was found to expedite the recovery of patients with acute non-specific pneumonia (Narimanian et al 2005).

Cancer therapy

A polypharmacy preparation known as AdMax®, which contains *Eleutherococcus senticosus* in combination with *Leuzea carthamoides*, *Rhodiola rosea* and *Schizandra chinensis*, has been shown to boost the suppressed immunity in patients with ovarian cancer who are subject to chemotherapy (Kormosh et al 2006). Which herb or combination of herbs is responsible for the effect is unclear.

OTHER USES

Given the herb's ability to increase levels of serotonin and noradrenaline in animal studies (Abramova et al 1972), a theoretical basis exists for the use of Siberian ginseng in depression.

In traditional Chinese medicine (TCM), Siberian ginseng is used to encourage the smooth flow of Qi and blood when obstructed, particularly in the elderly, and is viewed as a general tonic. It is therefore used for a myriad of indications, usually in combination with other herbal medicines. Numerous studies use Siberian ginseng in combination with other adaptogens, such as *Rhodiola rosea* and *Schisandra chinensis*, which may potentially act synergistically for improved effects.

DOSAGE RANGE

- 1–4 g/day dried root or equivalent preparations.
- Fluid extract (1:2): 2–8 mL/day (15–55 mL/week).
- Tincture (1:5): 10–15 mL/day.
- Acute dosing: 4 mL in a single dose before activity.
- Extracts with standardised levels of eleutheroside E (syringin) (> 0.5 mg/mL) are recommended. Russian and Korean sources appear to have higher levels of this constituent. So, variations in therapeutic activity may be predicted (Wagner et al 1982). As there can be a significant product variability in the level of eleutherosides between capsules and liquids, standardisation may be necessary for quality assurance (Harkey et al 2001).

In practice, Siberian ginseng is often given for 6 weeks with a break of at least 2 weeks before resuming treatment.

Clinical note — Case reports of Siberian ginseng need careful consideration

Some adverse reactions attributed to Siberian ginseng have subsequently been found to be due to poor product quality, herbal substitution and/or interference with test results. For example, initial reports linking maternal ginseng use to neonatal androgenisation are now suspected to be due to substitution with another herb, *Periploca sepium* (called Wu jia or silk vine), as American herb companies importing Siberian ginseng from China have been known to be supplied with two or three species of *Periploca* (Awang 1991). Additionally, rat studies have failed to detect significant androgenic action (Awang 1991, Waller et al 1992) for Siberian ginseng.

Another example is the purported interaction between digoxin and Siberian ginseng, which was based on a single case report of a 74-year-old man found to have elevated digoxin levels for many years (McRae 1996). It was subsequently purported that the herbal product may have been adulterated with digitalis. Additionally, Siberian ginseng contains glycosides with structural similarities to digoxin that may modestly interfere with digoxin fluorescence polarisation (FPIA), microparticle enzyme (MEIA) results, falsely elevating digoxin values with FPIA and falsely lowering digoxin values with MEIA (Dasgupta & Reyes 2005). It should be noted that measuring free digoxin does not eliminate these modest interferences in serum digoxin measurement by the Digoxin III assay (Dasgupta et al 2008).

ADVERSE REACTIONS

Clinical trials of a 6 months' duration have shown no side effects from treatment (Bohn et al 1987). High doses may cause slight drowsiness, irritability, anxiety, mastalgia, palpitations or tachycardia, although these side effects may be more relevant to *Panax ginseng*.

It is suggested that a spontaneous subarachnoid haemorrhage in a 53-year-old woman who was using an herbal supplement containing red clover, dong quai and Siberian ginseng was likely to be due to the dong quai (Friedman et al 2007).

SIGNIFICANT INTERACTIONS

As controlled studies are not available, interactions are currently speculative and based on evidence of pharmacological activity and case reports. Studies have reported that normal doses of Siberian ginseng are unlikely to affect drugs metabolised by CYP2D6 or CYP3A4 (Donovan et al 2003).

Anticoagulants

An in-vivo study demonstrated that an isolated constituent in Siberian ginseng has anticoagulant activity (Yun-Choi et al 1987), and a clinical trial found a reduction in blood coagulation induced by intensive training in athletes (Azizov 1997). Whether these effects also occur in nonathletes is unknown. Given that a study looking at the concomitant application of Kan Jang (Siberian ginseng in combination with andrographis) and warfarin did not produce significant effects on the pharmacokinetics or pharmacodynamics of the drug (Hovhannisyan et al 2006), a negative clinical effect is unlikely.

Chemotherapy

An increased tolerance for chemotherapy and improved immune function has been demonstrated in women with breast (Kupin 1984, Kupin & Polevaia 1986) and ovarian (Kormosh et al 2006) cancer undergoing chemotherapy treatment. Caution — as coadministration may theoretically reduce drug effects. However, beneficial interaction may be possible under medical supervision.

Diabetic medications

Claims that Siberian ginseng has hypoglycaemic effects are based on intravenous use in animal studies and not observed in humans for whom oral intake may actually increase postprandial glycaemia (Sievenpiper et al 2004). Observe diabetic patients taking ginseng.

Influenza virus vaccine

Ginseng may reduce the risk of post-vaccine reactions (Zykov & Protasova 1984), a possible beneficial interaction.

CONTRAINDICATIONS AND PRECAUTIONS

Some authors suggest that high-dose Siberian ginseng should be avoided by those with cardiovascular disease or hypertension (blood pressure (BP) > 80/90 mmHg) (Mahady et al 2000). Others merely suggest a caution, as reports are largely unsubstantiated (Holford & Cass 2001). As such, it is recommended that people with hypertension should be monitored

PRACTICE POINTS/PATIENT COUNSELLING

- Siberian ginseng appears to alter the levels of different neurotransmitters and hormones involved in the stress response, chiefly at the HPA axis.
- It is widely used to treat individuals with nervous exhaustion or anxiety due to chronic exposure to stress or what are now termed 'allostatic load situations'. It is also recommended during convalescence or fatigue to improve mental and physical responses.
- Siberian ginseng may increase resistance to infection and has been shown to reduce frequency of genital herpes outbreaks with long-term use.
- The herb is popular among athletes in the belief that endurance, performance and power may improve with its use, but clinical studies have produced inconsistent results.
- It is not recommended for use in pregnancy, and people with hypertension should be monitored if using high doses.

if using high doses. In a study of elderly people with hypertension, 8 weeks of Siberian ginseng use did not affect BP control (Cicero et al 2004).

Due to possible effects on glycaemic control (Sievenpiper et al 2004), care should be taken in people with diabetes until safety is established. Suspend use 1 week before major surgery.

Traditional contraindications include hormonal changes, excess energy states, fever, acute infection, concurrent use of other stimulants and prolonged use.

PREGNANCY USE

Insufficient reliable information is available, but the herb is not traditionally used in pregnancy.

PATIENTS' FAQs

What will this herb do for me?

Siberian ginseng affects many chemicals involved in switching on and off the body's stress responses. As such, it is used to improve wellbeing during times of chronic stress; however, scientific research has yet to fully investigate its use in this regard. It may also boost immune function and reduce the frequency of genital herpes outbreaks. Evidence for improved performance in athletes is unconvincing.

When will it start to work?

Effects on stress levels should develop within 6 weeks, whereas immune responses develop within 30 days.

Are there any safety issues?

It should not be used in pregnancy, and high doses should be used with care by those with hypertension.

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Globe artichoke

HISTORICAL NOTE Artichoke has a long history of use as a vegetable delicacy and medicinal agent, and its cultivation in Europe dates back to ancient Greece and Rome. It was domesticated in Roman times, possibly in Sicily, and spread by the Arabs during early Middle Ages. Traditional use of artichoke has always pertained to the liver where it is considered to increase bile flow and act as a protective agent against various toxins. As such, it has been used for jaundice, dyspepsia, nausea, gout, pruritis and urinary stones. It is still a popular medicine in Europe today.

COMMON NAME
Artichoke

OTHER NAMES
Alcachofa, artichaut, alcaucil, carciofo, cynara

BOTANICAL NAME/FAMILY
Cynara scolymus L. (family [Compositae] Asteraceae)

PLANT PART USED
Leaf

CHEMICAL COMPONENTS
Key constituents of the leaf include phenolic acids, mainly caffeic acid derivatives (e.g. chlorogenic acid), sesquiterpenes, lactones (e.g. cynaropicrin) and flavonoids (e.g. cynaroside, luteolin derivatives, anthocyanin), phytosterols, inulin and free luteolin.

MAIN ACTIONS
The main pharmacologically active constituents are thought to be the phenolic acids and flavonoids.

Antioxidant
Artichoke leaf extract exerts antioxidant effects, according to in vitro and clinical studies (Skarpanska-Stejnborn et al 2008, Speroni et al 2003). According to a double-blind trial, oral globe artichoke (400 mg three times daily) significantly elevates plasma total antioxidant capacity compared to placebo (Skarpanska-Stejnborn et al 2008). Studies further confirm the bioavailability of the metabolites of hydroxycinnamic acids after ingestion of cooked edible globe artichoke (Azzini et al 2007).

Hepatoprotective
Improved hepatic regeneration, improved hepatic blood flow, increased hepatocyte counts, increased hepatic RNA concentrations and a stimulation of hepatic cytogenesis have been associated with artichoke extract in animal studies (Ursapharm Arzneimittel 1998).

Tests with primary hepatocyte cultures and animal models indicate that artichoke extracts have marked antioxidative and hepatoprotective potential (Gebhardt 1997, Mehmetcik et al 2008, Miccadei et al 2008).

Choleretic and cholagogue
A significant increase in bile flow has been demonstrated in studies using isolated perfused rat liver in vivo after acute treatment, as well as after repeated administration (Saenz et al 2002). Choleretic activity has also been reported in a double-blind, placebo-controlled study, with maximal effects on mean bile secretion observed 60 min after a single dose (Kirchhoff et al 1994).

A study that evaluated the effects of four extracts and phenolic content on bile flow and liver protection demonstrated that the extract with the highest concentration of phenolic derivatives exerted the strongest effect (Speroni et al 2003).

One study determined that treatment does not produce changes to the liver enzymes gamma glutamyl transpeptidase (GGTP), aspartate transaminase (AST), alanine transaminase (ALT) or glutamic dehydrogenase (Pittler et al 2002).

Diuretic
Artichoke administration stimulated urine excretion in animal studies (Ursapharm Arzneimittel 1998).

Lipid-lowering
Artichoke leaf extract inhibited cholesterol biosynthesis in primary cultured rat hepatocytes (Gebhardt 1998) and indirect modulation of hydroxymethylglutaryl-CoA-reductase activity is the most likely inhibitory mechanism. When several known constituents were screened for activity, cynaroside, and particularly its aglycone luteolin, were mainly responsible for the effect. These results have been confirmed recently (Gebhardt 2002). Clinical studies have found that artichoke leaf extract causes a modest but statistically significant reduction in total cholesterol (Bundy et al 2008, Skarpanska-Stejnborn et al 2008).

OTHER ACTIONS
Artichoke administration had beneficial effects on lowering blood glucose levels in alloxan-treated rabbits (Ursapharm Arzneimittel 1998). Studies using artichoke leaf juice showed that it improved endothelial reactivity, most likely by its antioxidant constituents (Juzyszyn et al 2008, Lupattelli et al 2004).

Artichoke leaves exhibit some antifungal activities in vitro (Zhu et al 2005).

According to German commission E, human studies have confirmed carminative, spasmolytic and antiemetic actions (Blumenthal et al 2000). The antispasmodic activity of some fractions and cynaropicrin, a sesquiterpene lactone from *Cynara scolymus*, has recently been confirmed in vivo (Emendorfer et al 2005).

In-vitro studies using the edible part of artichoke exerted apoptotic activity on a human liver cancer cell line (Miccadei et al 2008).

Clinical note — Inulin: a natural prebiotic
Inulin is a plant-derived carbohydrate that is not digested or absorbed in the small intestine, but is fermented in the colon by beneficial bacteria. It functions as a prebiotic, stimulating growth of bifidobacteria in the intestine and has been associated with the enhanced function of the gastrointestinal system and immune system (Lopez-Molina et al 2005). Increasing levels of beneficial bacteria, such as bifidobacteria, allow them to 'out compete' potentially detrimental organisms and improve the health of the host. Inulin also increases calcium and magnesium absorption, influences blood glucose levels and reduces the levels of cholesterol and serum lipids. Globe artichoke contains 3% of fresh-weight inulin and smaller amounts are found in the leaves. According to animal studies, this concentration is sufficient to favourably affect the intestinal health (Goñi et al 2005).

CLINICAL USE

Hyperlipidaemia

Data are available from both controlled and uncontrolled studies that have investigated the effects of artichoke leaf extract in hyperlipidaemia. Most studies use Hepar SL forte® or Valverde Artischoke bei Verdauungsbeschwerden (artichoke dry extract) containing 450 g of herbal extract as a coated tablet.

Overall, evidence from five uncontrolled studies, case series and placebo-controlled trials suggests that artichoke leaf extract and cynarin have lipid-lowering effects and a possible role as adjunctive therapy in hyperlipidaemia (Ulbricht & Basch 2005).

A Cochrane systematic review that analysed the results of two controlled studies concluded that artichoke leaf extract appears to have a modest positive effect on the levels of total cholesterol and LDL; however, there is insufficient evidence to recommend it as a treatment option for hypercholesterolaemia and trials with larger sample sizes are still required (Pittler et al 2002).

One of the studies was a randomised, placebo-controlled, double-blind, multicentre trial involving 143 subjects with total cholesterol levels > 7.3 mmol/L (> 280 g/dL) (Englisch et al 2000). A dose of 1800 mg artichoke leaf extract was administered daily for 6 weeks. Active treatment resulted in 18.5% decrease in serum cholesterol compared with 8.6% for placebo, a result that was significant. No differences were observed between the groups for blood levels of either HDL or triglycerides. Although dietary habits were recorded, the food intake was not strictly controlled in the entire patient sample. The second randomised, placebo-controlled, double-blind study involved 44 healthy volunteers and compared 1920 mg artichoke extract daily to placebo over a 12-week treatment period. No significant effects on serum cholesterol levels were observed in this study; however, subgroup analyses suggested that patients with higher initial total cholesterol levels experienced a significant reduction in total cholesterol levels compared to placebo.

Two placebo-controlled clinical studies were published, which further demonstrated modest but significant reductions in total cholesterol for artichoke leaf extract. Bundy et al (2008) conducted a 12-week, randomised study of 75 adults which found that treatment with artichoke leaf (1280 mg of a standardised extract) significantly reduced plasma total cholesterol by an average of 4.2% (from 7.16 mmol/L (SD 0.62) to 6.86 mmol/L (SD 0.68)) compared with controls, although no significant differences were observed for LDL cholesterol, HDL cholesterol or triglyceride levels.

A smaller randomised, double-blind study of 22 volunteers found that oral artichoke leaf extract (400 mg three times daily) significantly reduced serum total cholesterol levels by the end of the 5-week study compared to placebo (Skarpanska-Stejnborn et al 2008).

European Scientific Co-operative of Phytotherapy (ESCOP) approves the use of artichoke leaf as an adjunct to a low-fat diet in the treatment of mild-to-moderate hyperlipidaemia (ESCOP 2003).

Dyspepsia

Artichoke leaf extract has been studied as a bile secretion stimulant and primarily recommended in this way for non-ulcer dyspepsia.

A double-blind, randomised, placebo-controlled trial of 247 patients with functional dyspepsia (persistent or recurrent pain or discomfort in the upper abdomen with one or more of the following symptoms: early satiety, postprandial fullness, bloating and nausea) found that treatment with two capsules of 320 mg artichoke leaf extract LI 220 (HeparSL® forte) taken three times daily significantly improved overall symptoms over the 6 weeks compared with the placebo (Holtmann et al 2003). Additionally, active treatment significantly improved global quality of life (QOL) scores compared with the placebo.

A randomised, open study of 454 subjects investigated the efficacy of a low-dose artichoke leaf extract (320 mg or 640 mg daily) on amelioration of dyspeptic symptoms and improvement of QOL (Marakis et al 2002). Both doses achieved a significant reduction of all dyspeptic symptoms, with an average reduction of 40% in global dyspepsia score. Although no differences in primary outcome measures were reported between the two treatment groups, the higher dosage resulted in greater improvements in anxiety.

An uncontrolled study of 553 patients with non-specific digestive disorders (dyspeptic discomforts, functional biliary colic and severe constipation) experienced a significant reduction of symptoms after 6 weeks of treatment with artichoke extract. Symptoms improved by an average of 70.5%, with strongest effects on vomiting (88.3%), nausea (82.4%), abdominal pain (76.2%), loss of appetite (72.3%), constipation (71.0%), flatulence (68.2%) and fat intolerance (58.8%). In 85% of patients, the global therapeutic efficacy of artichoke extract was judged by the physicians as excellent or good (Fintelmann 1996).

The German Commission E approves artichoke leaf and preparations made from artichoke leaf as a choleretic agent for dyspeptic problems (Blumenthal et al 2000).

Irritable bowel syndrome (IBS)

Artichoke leaf extract appears to have substantial benefits in IBS, according to the available evidence; however, large controlled studies are required to confirm these observations. The antispasmodic and probiotic activities of artichoke leaf are likely to contribute to the beneficial effects produced by this preparation.

A subgroup of patients with IBS symptoms was identified from a sample of subjects with dyspeptic syndrome who were being monitored for 6 weeks (Walker et al 2001). Analysis of the data revealed 96% of patients rated artichoke leaf extract as better than or at least equal to previous therapies administered for their symptoms. Physicians also provided favourable reports on its effects in these patients.

A study of 208 adults with IBS observed before and after a 2-month intervention period of changes in symptoms (Bundy et al 2004). A significant reduction in the incidence of IBS by 26.4% and a significant shift in self-reported usual bowel pattern towards 'normal' were also reported after treatment. The Nepean Dyspepsia Index (NDI) total symptom score significantly decreased by 41% after treatment and there was a significant 20% improvement in the NDI total QOL score.

Reducing alcohol-induced hangover

Artichoke extract does not prevent the signs and symptoms of alcohol-induced hangover in healthy adults, according to a small randomised, double-blind, crossover trial (Pittler et al 2003). The dose used in the study was 960 mg taken immediately before and after consuming alcohol for 2 days. The same researchers later conducted a systematic review to assess the clinical evidence on the effectiveness of any medical intervention for preventing or treating alcohol hangover and found that no compelling evidence exists (Pittler et al 2005).

OTHER USES

Traditional uses include treatment for jaundice, dyspepsia, nausea, gout, pruritis and urinary stones. Due to its choleretic effect, it has also been used to improve digestion of fats.

Wild artichoke (*C. cardunculus*) significantly restores proper vasomotion after simulation of oxidative stress in rat models. This may have clinical significance for treatment in the elderly, where a progressive loss of vascular endothelial function and concurrent loss of vasomotor control is frequent (Rossoni et al 2005). The antioxidant activity of artichoke has been shown to offer a protective effect on gonads of cadmium-treated rats (Gurel et al 2007).

DOSAGE RANGE

- 1:2 liquid extract: 3–8 mL/day in divided doses.
- 6 g daily of dried cut leaves, pressed juice of the fresh plant or equivalent.

According to clinical studies

- Hyperlipidaemia: 4–9 g/day of dried leaves or 1800 mg/day artichoke leaf extract.
- Dyspepsia: artichoke leaf extract 640 mg/day.
- IBS: artichoke leaf extract 640 mg/day.

ADVERSE REACTIONS

Studies with hyperlipidaemic subjects indicate that globe artichoke leaf extract is generally well tolerated. Mild symptoms of flatulence, hunger and weakness were reported in approximately 1% of subjects when the fresh plant was used (Fintelmann 1996). Contact dermatitis is possible with the fresh plant and urticaria–angio-oedema has been reported in one case of ingestion of raw and boiled herb (Mills & Bone 2005).

SIGNIFICANT INTERACTIONS

None known.

CONTRAINDICATIONS AND PRECAUTIONS

Not to be used by people with known allergy to globe artichoke or other members of the Asteraceae/Compositae family of plants.

Herbs with choleretic and cholagogue activities should be used with caution by people with bile duct obstruction (Blumenthal et al 2000), acute or severe hepatocellular disease (e.g. cirrhosis), septic cholecystitis, intestinal spasm or ileus, liver cancer or with unconjugated hyperbilirubinaemia (Mills & Bone 2005).

PREGNANCY USE

Safety has not been scientifically established for the leaf extract. Dietary intake is likely to be safe.

PRACTICE POINTS/PATIENT COUNSELLING

- Artichoke leaf extract has antioxidant, choleretic, diuretic, antispasmodic and lipid-lowering activity and possibly hepatoprotective and antiemetic effects.
- According to controlled clinical trials, artichoke extract has a modest but significant effect in lowering total cholesterol levels although effects on other blood lipids are less consistent. ESCOP recommends that a low-fat diet should also be undertaken when artichoke leaf extract is used for mild-to-moderate hyperlipidaemia.
- Artichoke leaf extract is an effective symptomatic treatment for non-ulcer dyspepsia and shows promise for IBS.
- The extract is well tolerated with few side effects, but should not be used by people with known allergy to globe artichoke or other members of the Asteraceae/Compositae family of plants and used with caution in bile duct obstruction, acute or severe hepatocellular disease (e.g. cirrhosis), septic cholecystitis, intestinal spasm or ileus, liver cancer or people with unconjugated hyperbilirubinaemia.

PATIENTS' FAQs

What will this herb do for me?

Artichoke leaf extract effectively reduces symptoms in non-ulcer dyspepsia and possibly IBS.

It also modestly reduces total cholesterol levels and improves digestion, flatulence and nausea.

When will it start to work?

Symptomatic relief in dyspepsia and IBS appear after 2–3 weeks of treatment; however, further improvements are possible with long-term use. A reduction in cholesterol may take 4–6 weeks and is best achieved when combined with a low-fat diet.

Are there any safety issues?

The extract is well tolerated with few side effects, but should not be used by people with known allergy to globe artichoke or other members of the Asteraceae/Compositae family of plants and used with caution in bile duct obstruction, acute or severe hepatocellular disease (e.g. cirrhosis), septic cholecystitis, intestinal spasm or ileus, liver cancer or people with unconjugated hyperbilirubinaemia.

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Glucosamine

OTHER NAMES

D-Glucosamine, amino monosaccharide, glucosamine sulfate, glucosamine hydrochloride, glucosamine hydroiodide, *N*-acetyl D-glucosamine, 2-amino-2-deoxy-beta-D-glucopyranose

BACKGROUND AND RELEVANT PHARMACOKINETICS

Glucosamine is a naturally occurring substance that is required for the production of proteoglycans, mucopolysaccharides and hyaluronic acid, which

are substances that make up joint tissue, such as articular cartilage, tendons and synovial fluid. It is also a component of blood vessels, heart valves and mucus secretions (Kelly 1998).

Glucosamine sulfate is 90% absorbed after oral administration. The bioavailability is approximately 20% after first-pass metabolism (Aghazadeh-Habashi et al 2002). Unbound glucosamine is concentrated in the articular cartilage and the elimination half-life is 70 h, with excretion as CO_2 in expired air, as well as by the kidneys and in faeces (Setnikar & Canali 1993). A study of the pharmacokinetics of glucosamine sulfate in humans found that it is rapidly absorbed after oral administration and its elimination half-life was tentatively estimated to average 15 h, therefore supporting once-daily dosing (Persiani et al 2005). Twice-daily dosing with 500 mg of a time-release formula has also been shown to provide comparable serum levels after 24 h as three divided doses of 500 mg (Basak et al 2004).

A further study suggests that glucosamine is bioavailable both systemically and at the joint, and that steady state concentrations in human plasma and synovial fluid were correlated and in line with levels deemed effective in in vitro studies (Persiani et al 2007). This is contrasted by the suggestion from a study of 18 people with osteoarthritis (OA) that found serum glucosamine levels were significantly less than those previously shown to have in vitro effects (Biggee et al 2006). Similar results were reported in an equine study that found levels attained in serum and synovial fluid were 500-fold lower than those reported to modify chondrocyte anabolic and catabolic activities in tissue and cell culture experiments (Laverty et al 2005).

CHEMICAL COMPONENTS

2-amino-2-deoxy-D-glucose

FOOD SOURCES

Glucosamine is present in chitin from the shells of prawns and other crustaceans. As a supplement, glucosamine is derived from marine exoskeletons or produced synthetically and is available in salt forms, including glucosamine sulfate, glucosamine hydrochloride, glucosamine hydroiodide and *N*-acetyl glucosamine. Glucosamine salts are likely to be completely ionised in the stomach, although clinical equivalence of the different salts has not been established. The purity and content of products has been questioned in the USA, where glucosamine is regarded as a food supplement and its quality is unregulated (Consumer Lab 2006).

MAIN ACTIONS

Chondroprotective effect

Glucosamine is a primary substrate and stimulant of proteoglycan biosynthesis and inhibits the degradation of proteoglycans. Glucosamine may also stimulate synovial production of hyaluronic acid, a compound responsible for the lubricating and shock-absorbing properties of synovial fluid (McCarty 1998a, McCarty et al 2000). Glucosamine promoted cell differentiation and increased alkaline phosphatase (ALP) activity, collagen synthesis, osteocalcin secretion and mineralisation in osteoblastic cells (Kim et al 2007) as well as caused a statistically significant stimulation of proteoglycan production by chondrocytes from human osteoarthritic cartilage culture (Bassleer et al 1998). Glucosamine sulfate has also been found to modify cultured OA chondrocyte metabolism by acting on protein kinase C, cellular phospholipase A_2, protein synthesis and possibly collagenase activation (Piperno et al 2000). *N*-acetyl glucosamine also has been found to produce proliferation of matured cartilaginous tissues and matured cartilage substrate in experimentally produced cartilaginous injuries in rabbits (Tamai et al 2003), and oral administration of glucosamine has been shown to have limited site-specific, partial disease-modifying effect in animal models of OA (Tiraloche et al 2005). In another animal model, co-administration with chondroitin was seen to prevent both biochemical and histological alterations and provide pain reduction (Silva et al 2009). Glucosamine may be a useful adjunct to intraarticular corticosteroid injections, as it was seen to protect equine chondrocytes from methylprednisolone-induced inhibition of proteoglycan synthesis in vitro (Byron et al 2008).

The results of one in vitro study suggest that the experimental effects of glucosamine are sensitive to the experimental model, the doses and length of treatment and that in the model using bovine chondrocytes, pharmacological doses of glucosamine induced a broad impairment in the metabolic activity of the chondrocytes, leading to cell death (de Mattei et al 2002).

Glucosamine was found to have no effect on type 2 collagen fragment levels in serum or urine in a 6-month RCT of 137 subjects with OA of the knee (Cibere et al 2005) and exogenous glucosamine was found not to stimulate chondroitin sulfate synthesis by human chondrocytes in vitro. Furthermore, these cells were found to have the capacity to form amounts of glucosamine from glucose far in excess of that provided by levels achievable through oral administration (Mroz & Silbert 2004).

It has been suggested that at least some of the chondroprotective action of glucosamine sulfate is due to the provision of a source of additional inorganic sulfur which is essential for glycosaminoglycan (GAG) synthesis as well as being a structural component of glutathione and other key enzymes, coenzymes and metabolites that play fundamental roles in cellular homeostasis and control of inflammation (Nimni & Cordoba 2006).

Anti-inflammatory

A number of in vitro and in vivo tests have identified anti-inflammatory activity for glucosamine. Anti-inflammatory and chondroprotective activities have been observed in human OA cartilage (Sumantran et al 2008). In vitro studies have found that glucosamine sulphate exerts anti-inflammatory effects by altering production of TNF-alpha, interleukins and prostaglandin E2 in macrophage cells (Kim et al 2007). Glucosamine and *N*-acetyl

glucosamine inhibit IL-1-beta- and TNF-alpha-induced NO production in normal human articular chondrocytes (Shikhman et al 2001). However glucosamine, but not *N*-acetyl glucosamine, inhibits human neutrophil functions such as superoxide generation, phagocytosis, granule enzyme release and chemotaxis (Hua et al 2002). Glucosamine restores proteoglycan synthesis and prevents the production of inflammatory mediators induced by the cytokine IL-1-beta in rat articular chondrocytes in vitro (Gouze et al 2001). Furthermore, glucosamine has been found to suppress PGE_2 production and partly suppress NO production in chondrocytes in vitro (Mello et al 2004, Nakamura et al 2004), as well as suppressing the production of matrix metalloproteases in normal chondrocytes and synoviocytes (Nakamura et al 2004).

Glucose metabolism

Exogenous glucosamine is actively taken up by cells. Its entry into cells is stimulated by insulin and involves the glucose transporter system (Pouwels et al 2001); however, the affinity of glucosamine for these transporters is substantially lower than that of glucose (Nelson et al 2000).

Early preliminary evidence suggested that glucosamine may cause changes in glucose metabolism and insulin secretion similar to those seen in type 2 diabetes in both rats (Balkan & Dunning 1994, Giaccari et al 1995, Lippiello et al 2000, Shankar et al 1998) and humans (Monauni et al 2000); however, these findings have been disputed (Echard et al 2001). In the 10 years following the original research, clinical trial evidence has accumulated which has failed to find any significant effect on glucose metabolism in humans (Anderson et al 2005, Tannis et al 2004).

Gastrointestinal protection

Glycoproteins are important in protecting the bowel mucosa from damage, and the breakdown of glycosaminoglycans is an important consequence of inflammation of mucosal surfaces (Salvatore et al 2000). Abnormalities in colonic glycoprotein synthesis have been implicated in the pathogenesis of ulcerative colitis and Crohn's disease (Burton & Anderson 1983, Winslet et al 1994).

OTHER ACTIONS

Glucosamine might have some activity against HIV. Preliminary evidence shows that it inhibits intracellular viral movement and blocks viral replication (Bagasra et al 1991). Other studies have found that glucosamine has immunosuppressive properties and can prolong graft survival in mice (Ma et al 2002). Oral, intraperitoneal and intravenously administered glucosamine significantly reduces CNS inflammation and demyelination in an animal model of multiple sclerosis (Zhang et al 2005).

CLINICAL USE

Osteoarthritis

There is strong evidence to suggest that glucosamine is effective in treating the symptoms of OA, as well as being effective in slowing disease progression. Reviews of clinical trials generally confirm the efficacy of glucosamine in providing pain relief from OA, although there are some inconsistent results (Bruyere & Reginster 2007, Reginster et al 2007, Vangsness et al 2009). A Cochrane review of 16 RCTs concluded that 'there is good evidence that glucosamine is both effective and safe in treating OA' and that 'glucosamine therapy may indeed represent a significant breakthrough in the pharmacological management of OA' (Towheed et al 2003). Although most studies have been of OA of the knee, there is some clinical evidence that it is also active against OA of the spine (Giacovelli & Rovati 1993), temporomandibular joint (Shankland 1998) and hands (Scarpellini et al 2008).

The first placebo-controlled clinical trials investigating glucosamine in OA were published in the early 1980s. Drovanti et al showed that a dose of 1500 mg glucosamine sulfate significantly reduced symptoms of OA, almost twice as effectively and twice as fast as placebo (Drovanti et al 1980). Perhaps the most exciting results were found when electron microscopy analysis of cartilage showed that those people taking glucosamine sulfate had cartilage more similar to healthy joints than the placebo group. Based on this finding, researchers suggested that glucosamine sulfate had not only provided symptom relief but also had the potential to induce rebuilding of the damaged cartilage.

Since that time, multiple human clinical trials lasting from a few weeks (Crolle & D'Este 1980, Drovanti et al 1980, Lopes Vaz 1982, McAlindon 2001, Pujalte et al 1980, Qiu et al 1998) to 3 years (Pavelka et al 2002, Reginster et al 2001), as well as systematic reviews (Poolsup et al 2005, Towheed et al 2003, 2006) and meta-analyses (McAlindon et al 2000, Richy et al 2003) have shown that glucosamine sulfate (1500 mg/day) can significantly improve symptoms of pain and functionality measures in patients with OA of the knee, with side effects comparable to those of placebo.

The National Institutes of Health (NIH) recently spent US$14 million on a Glucosamine Chondroitin Arthritis Intervention Trial (GAIT), a 24-week, placebo-controlled, parallel, double-blind, five-arm trial involving 1583 patients that aimed to answer the question as to the efficacy of glucosamine hydrochloride and chondroitin by comparing glucosamine alone, glucosamine plus chondroitin, chondroitin alone, placebo and the COX-2 inhibitor celecoxib (Clegg et al 2006, NIH 2002). The results of this study provide good evidence that glucosamine and chondroitin are more effective when given in combination than when either substance is given alone and that combined treatment with glucosamine and chondroitin is more effective than celecoxib for treating moderate-to-severe, but not mild, arthritis. The design of the GAIT trial can be criticised for the fact that it included a large number of people with very mild disease who were more likely to be susceptible to placebo (as evidenced by the very high (60%) placebo response). Furthermore, the criteria for effectiveness was set very high (20% reduction in Western Ontario and McMaster Osteoarthritis Index (WOMAC) pain score)

and that when the internationally accepted Outcome Measures in Rheumatology-Osteoarthritis Research Society International (OMERACT-OARSI) response criteria for judging clinical trials of OA was used, the combined treatment was significantly better than placebo for patients with either mild or moderate-to-severe disease (Clegg et al 2006).

In addition to providing symptomatic relief from OA, there is evidence from two long-term (3-year) studies (Pavelka et al 2002, Reginster et al 2000) and two year-long studies of glucosamine and chondroitin (Rai et al 2004, Scarpellini et al 2008) that glucosamine also slows disease progression. Reginster et al (2000) compared the effects of 1500 mg glucosamine sulfate with placebo daily over 3 years in 212 patients aged over 50 years with primary knee OA. This was heralded as a landmark study at the time because it not only detected modest symptom-relieving effects, but also was the first to identify significant joint-preserving activity with long-term use. Two years later, Pavelka et al confirmed these results in another randomised, double-blind study that involved 202 patients with knee OA (Pavelka et al 2002) and once again observed that long-term treatment with glucosamine sulfate retarded disease progression. A post hoc analysis of these studies found that the disease-modifying effect was evident in 319 postmenopausal women (Bruyere et al 2004) and another subanalysis found that patients with less severe radiographic knee OA, who are likely to experience the most dramatic disease progression, may be particularly responsive to treatment with glucosamine (Bruyere et al 2003). A 1-year trial involving 104 subjects with OA of the hands, hip and knee found that treatment with both glucosamine and chondroitin reduced pain and significantly slowed disease progression as measured by radiographs and measures of urinary C-terminal cross-linking telopeptides of type I collagen (Scarpellini et al 2008). In contrast to the above findings, a 24-month, double-blind, placebo-controlled study of 572 patients conducted as part of the GAIT study did not demonstrate reductions in joint space narrowing, although there was a trend for improvement in knees with Kellgren and Lawrence (K/L) grade 2 radiographic OA. The authors state, however, that power of this study was diminished by the limited sample size, variance of joint space width (JSW) measurement and a smaller than expected loss in joint space (Sawitzke et al 2008).

A study suggests that treatment with glucosamine sulfate for at least 12 months results in significant reduction in health resource utilisation even after treatment is discontinued. This study which involved 275 subjects previously involved in 12-month glucosamine intervention trials followed subjects for up to 5 years after treatment was discontinued (making up a total of 2178 patient-years of observation). The study showed that total knee replacement had occurred in over twice as many patients from the placebo group (19/131 or 14.5%), than in those formerly receiving glucosamine sulphate (9/144 or 6.3%) (Bruyere et al 2008).

Not all clinical trials of glucosamine for OA have produced positive results. A 2-year randomised controlled trial of 222 patients with hip OA who received either 1500 mg of oral glucosamine sulfate or placebo daily found no difference in WOMAC scores or joint space narrowing after 24 months (Rozendaal et al 2008). Similarly a 12-week, double-blind, randomised, placebo-controlled trial of glucosamine performed over the internet involving 205 subjects with symptomatic knee OA found no difference in pain, stiffness, analgesic use or physical function between the glucosamine and placebo groups (McAlindon et al 2004). In another 6-month randomised, double-blind, placebo-controlled study of glucosamine sulfate in knee OA there was no significant difference in the time to disease flare, symptoms or analgesic medication use between the glucosamine and placebo groups (Cibere et al 2004). A further controlled trial of 80 OA patients using glucosamine sulfate over 6 months found no difference between the glucosamine group and placebo for symptoms, except for a small but significant difference in knee flexion, which was suggested to be caused by measurement error (Hughes & Carr 2002). Further studies suggest that glucosamine either alone or in combination with chondroitin offered no additional benefit to exercise in people with OA of the knee (Messier et al 2007, Kawasaki et al 2008).

Theories to explain inconsistencies

It has been suggested that the type of glucosamine preparation, inadequate allocation concealment and industry bias may account for the inconsistent results seen in glucosamine trials. A study of 15 separate trials suggests that glucosamine hydrochloride is not effective (effect size 0.06) while glucosamine sulfate is effective (effect size 0.44) and that other than allocation concealment there were no study design features that could explain differences between studies. It is further suggested that differences may be a result of industry bias (Vlad et al 2007). Most clinical trials have used a specific patented oral formulation of glucosamine sulfate from Rottapharm, Italy, which is available as a prescription medicine in Europe. Although other forms of glucosamine are used in practice, there is significantly more evidence supporting the use of glucosamine sulfate than others (Reginster et al 2005, Vlad et al 2007, Felson 2008). An updated Cochrane review that looked at 20 studies involving a total of 2570 patients found that studies using a non-Rottapharm preparation failed to show benefit in pain and function, whereas studies of the Rottapharm preparation found glucosamine to be superior to placebo in the treatment of pain and functional impairment (Towheed et al 2006).

Combination therapy

Chondroitin sulfate and glucosamine are frequently marketed together in combination products and some studies suggest that this combination is effective in treating symptoms (Clegg et al 2006, Das & Hammad 2000, Leffler et al 1999, McAlindon et al 2000, Nguyen et al 2001, NIH 2002) and reducing

joint space narrowing (Rai et al 2004). This is supported by an in vitro study of horse cartilage, which found that a combination of glucosamine and chondroitin was more effective than either product alone in preventing articular cartilage glycosaminoglycan degradation (Dechant et al 2005). Further support for combination therapy comes from an in vivo study of rats, which found that combined treatment with chondroitin and glucosamine prevented the development of cartilage damage and was associated with a reduction in IL-1-beta and matrix metalloprotease-9 synthesis (Chou et al 2005).

Although glucosamine has not been shown to have direct analgesic activity, certain combinations with non-opioid analgesics have demonstrated synergistic (e.g. ibuprofen and ketoprofen), additive (e.g. diclofenac, indomethacin, naproxen and piroxicam) or subadditive (e.g. aspirin and paracetamol) antinociceptive interactions in the mouse abdominal irritant test, suggesting that combinations of certain ratios of glucosamine and specific non-steroidal anti-inflammatory drugs (NSAIDs) might enhance pain relief or provide adequate pain relief with lower doses of NSAIDs (Tallarida et al 2003).

In a 12-week, randomised, placebo-controlled trial of glucosamine and methylsulfonylmethane involving 118 patients, combined therapy was found to produce a greater and more rapid reduction in pain, swelling and loss of function than either agent alone (Usha & Naidu 2004).

In an in vivo study of arthritic rats, the combination of glucosamine and essence of chicken was more effective in reducing the histopathological severity of arthritis than glucosamine alone (Tsi et al 2003).

A topical preparation containing glucosamine with chondroitin and camphor has been shown to reduce pain from OA of the knee in one randomised controlled trial (Cohen et al 2003).

Comparisons with NSAIDs

There are many studies suggesting that glucosamine is at least as effective as NSAIDs in treating the symptoms of OA (Herrero-Beaumont et al 2007, Muller-Fassbender et al 1994, Reichelt et al 1994, Rovati 1992, Ruane & Griffiths 2002), although glucosamine has a slower onset of action, taking 2–3 weeks to establish an effect. The GAIT trial (see earlier) found that the combination of glucosamine and chondroitin was more effective than celecoxib in treating moderate to severe OA, whereas glucosamine alone was not (Clegg et al 2006).

Inflammatory bowel disease

In vitro and in vivo studies suggest that glucosamine may be useful in treating inflammatory bowel disease with in vitro studies demonstrating suppression of cytokine-induced activation of intestinal epithelial cells and in vivo studies finding that glucosamine improved clinical symptoms and suppressed colonic inflammation and tissue injury in a rat model of inflammatory bowel diseases (Yomogida et al 2008). The anti-inflammatory activity of glucosamine is partly mediated by an increased production of heparan sulfate proteoglycans by the vascular endothelium, thereby improving the endothelium's barrier function (McCarty 1998b). It is possible that the step in glycoprotein synthesis involving the amino sugar is relatively deficient in patients with inflammatory bowel disease and this could reduce the synthesis of the glycoprotein cover that protects the mucosa from damage by bowel contents (Burton & Anderson 1983, Winslet et al 1994). In a pilot study, *N*-acetyl glucosamine proved beneficial in children with chronic inflammatory bowel disease (Salvatore et al 2000).

OTHER USES

Glucosamine demonstrates benefits in alleviating symptoms of degenerative joint disease in both horses (Forsyth et al 2006) and dogs (McCarthy et al 2007). There is the suggestion that glucosamine may provide symptomatic relief for people with rheumatoid arthritis; however, controlled studies are not available to confirm clinical effectiveness (Nakamura et al 2007).

It has been suggested that glucosamine may be a suitable cosmetic ingredient for use in skin care products. Because of its stimulation of hyaluronic acid synthesis, glucosamine has been shown to accelerate wound healing, improve skin hydration and decrease wrinkles. In addition, as an inhibitor of tyrosinase activation, it inhibits melanin production and is useful in treatment of disorders of hyperpigmentation (Bissett 2006). This is supported by an 8-week, double-blind, placebo-controlled trial, which found that hyperpigmentation was reduced with topical use of *N*-acetyl glucosamine with the effect being enhanced by niacinamide (Bissett et al 2007).

DOSAGE RANGE

- 1500 mg glucosamine/day (500 mg three times daily).
- A 2–3-month trial is generally used to determine whether it is effective for an individual patient.
- Intramuscular glucosamine sulfate: 400 or 800 mg three times/week (Reichelt et al 1994) for 4–6 weeks or longer if required.
- Glucosamine sulfate, hydrochloride, hydroiodide and *N*-acetyl forms are available. Most research has been done on the sulfate forms. Topical, intravenous, intramuscular and intraarticular forms are also available in some countries.

ADVERSE REACTIONS

Glucosamine has been used safely in multiple clinical trials lasting from 4 weeks to 3 years with minimal or no adverse effects (Lopes Vaz 1982, Pavelka et al 2002, Pujalte et al 1980, Reginster et al 2001). A 2006 Cochrane systematic review concluded that glucosamine is as safe as placebo (Towheed et al 2006). Glucosamine has an observed safe level (OSL) of 2000 mg/day.

Glucosamine sulphate has no significant effect on serum lipids (Albert et al 2007, Østergaard et al 2007). There is one case report of asthma

Clinical note — Should people with diabetes avoid glucosamine?

Clinicians' concern about the safety of glucosamine in diabetes were probably first fuelled by an article published in Lancet in 1999 (Adams 1999). The article entitled 'Hype about glucosamine' by Adams stated that glucosamine increases glucose resistance in normal and in experimentally diabetic animals (McClain & Crook 1996) and intravenous glucosamine in doses as low as 0.1 mg/kg/min result in a 50% reduction in the rate of glucose uptake in skeletal muscle (Baron et al 1995). Adams concluded by suggesting that perhaps all people, but especially those who are overweight or have diabetes, should be urged to have caution when using glucosamine. Nearly 10 years after the Adams article was published, a much larger body of evidence has accumulated which indicates that such concerns are not necessary.

In 2005, a critical review of clinical trial data for 3063 human subjects concluded that glucosamine does not affect glucose metabolism, there are no adverse effects of oral glucosamine administration on blood, urine or faecal parameters and side effects are significantly less common with glucosamine than with placebo or NSAIDs (Anderson et al 2005). Thirty-three studies were evaluated which included both diabetic and non-diabetic subjects. Twenty-eight studies were randomised, controlled trials; one study was controlled and five were observational trials. Sixteen chronic studies evaluated fasting plasma glucose levels and included 854 subjects followed for a weighted average of 37 weeks. Additionally, 26 studies used glucosamine sulphate and doses ranged from 1500 mg to 3200 mg daily.

being exacerbated by glucosamine–chondroitin supplementation (Tallia & Cardone 2002).

SIGNIFICANT INTERACTIONS

Controlled studies are not available so interactions remain speculative and are based on evidence of pharmacological activity.

Non-steroidal anti-inflammatory drugs

Glucosamine may theoretically enhance the anti-inflammatory activity of NSAIDs — drug dosage may require modification after several weeks' glucosamine use — a potentially beneficial combination.

CONTRAINDICATIONS AND PRECAUTIONS

Although there is a theoretical link between glucosamine and insulin resistance, this has not been demonstrated in human trials. Nevertheless, diabetics using glucosamine should have their blood sugar levels checked regularly.

Glucosamine is made from shellfish and, although it is not extracted from the protein component and appears to pose no threat to shrimp-allergic individuals (Villacis et al 2006), it should be used with caution in patients with shellfish allergy.

PRACTICE POINTS/PATIENT COUNSELLING

- Glucosamine is a naturally occurring building block of joint tissue and cartilage.
- Glucosamine is considered effective in treating the pain and disability of OA and it may act to slow the progression of the disease, although several weeks are required before a clinical effect is evident. The effects appear to be most consistent for glucosamine sulfate.
- It is considered extremely safe and may reduce the need for NSAIDs (which can have serious side effects).
- Glucosamine may have better clinical effects when used in conjunction with chondroitin.
- People with severe shellfish allergy should be advised to use a form that is not derived from shellfish.
- Patients with diabetes should monitor their blood glucose levels while taking glucosamine, although no significant changes are anticipated.

PREGNANCY USE

Insufficient reliable information is available to advise on safety in pregnancy. Some limited data suggest no increased risk for major malformations or other adverse fetal effects with glucosamine use during pregnancy (Sivojelezova et al 2007).

PATIENTS' FAQs

What will this supplement do for me?

Multiple scientific studies have shown that glucosamine sulfate reduces symptoms of OA and may also reduce further progression of the condition. Some people find that they do not require NSAIDs as often when taking it.

When will it start to work?

Symptom relief generally takes 2–3 weeks to establish, but joint protection effects occur only with long-term use of several years.

Are there any safety issues?

Although considered very safe for the general population, it should be used with caution in people with severe shellfish allergies.

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L-Glutamine

HISTORICAL NOTE Glutamine and glutamate were originally described in the mid-19th century and their functions began to be examined in the early 20th century. The role of glutamine in the immune system and gastrointestinal tract has been investigated since the 1980s.

BACKGROUND AND RELEVANT PHARMACOKINETICS

L-Glutamine (L-Gln) is a conditionally essential amino acid found in all life forms and the most abundant amino acid in the human body. During conditions of metabolic stress characterised by catabolism and negative nitrogen balance, such as trauma (including surgical trauma), prolonged stress, glucocorticoid use, excessive exercise, starvation, infection, sepsis, cancer and severe burns, the body is unable to synthesise L-Gln in sufficient quantities to meet biological needs and it becomes essential to have an exogenous intake (Miller 1999, PDRHealth 2006a).

L-Glutamine is absorbed from the lumen of the small intestine by active transport (Meng et al 2003) and is then transported to the liver via the portal circulation and enters systemic circulation, where it is distributed to various tissues and transported into cells via an active process. Elimination occurs via glomerular filtration and it is almost completely reabsorbed by the renal tubules. Some metabolism of L-Gln takes place in the enterocytes and hepatocytes and it is involved in various metabolic activities, including the synthesis of L-glutamate (catalysed by glutaminase), proteins, glutathione, pyrimidine and purine nucleotides and amino sugars. L-glutamate is converted to L-glutamine by glutamine synthase in the presence of ammonia, ATP and magnesium or manganese.

L-Glutamine is predominantly synthesised and stored in skeletal muscles where it comprises around 60% of the free amino acids and makes up 4–5% of muscle protein. In times of metabolic stress, glutamine is released into circulation and transported to tissues in need (Kohlmeier 2003, Miller 1999, PDRHealth 2006a).

Unfortunately L-Gln is not very soluble or stable in solution, especially upon heating for sterilisation, and as a result, until recently, was not included in total parenteral nutrition (TPN). The more soluble and stable glutamine dipeptides are now commonly used as the delivery forms in TPN solutions and some nutritional supplements (Kohlmeier 2003, PDRHealth 2000b).

Common forms available

The terms L-glutamine and glutamine are often used interchangeably. L-glutamine is the amide form of L-glutamic acid and contains 15.7% nitrogen (Kohlmeier 2003). It is also known as 2-aminoglutaramic acid, levoglutamide, (S)-2,5-diamino-5-oxopentaenoic acid and glutamic acid 5-amide.

Two synthetic glutamine dipeptides that may be used in TPN are L-alanyl-L-glutamine (Ala-Gln) and glycyl-L-glutamine (Gly-Gln). D-Glutamine, the stereoisomer of L-glutamine, has no known biological activity (Kohlmeier 2003, PDRHealth 2006b).

Since the late 1960s, L-Gln has been manufactured for pharmaceutical use using a fermentation broth. The manufacture of high-quality, low-cost L-Gln requires a strain of microorganism with good production efficiency and minimum by-products. Impurities can then be removed from the broth using a nanofiltration membrane to obtain a fine crystalline powder (Kusumoto 2001, Li et al 2003).

FOOD SOURCES

Typical dietary intake of L-Gln is 5–10 g/day (Miller 1999). Sources include animal and plant proteins, vegetable juices (especially cabbage), eggs, wheat, soybeans and fermented foods, such as miso and yoghurt (Kohlmeier 2003, PDRHealth 2006a).

DEFICIENCY SIGNS AND SYMPTOMS

Although traditionally considered a nonessential amino acid, L-Gln is now considered 'conditionally essential' during periods of metabolic stress characterised by catabolism and negative nitrogen balance.

Critical illness, stress and injury can lead to a significant decrease in plasma levels of L-Gln, which if severe, can increase the risk of mortality (Boelens et al 2001, Wischmeyer 2003).

Prolonged protein malnutrition may cause growth inhibition, muscle wasting and organ damage (Kohlmeier 2003). In the absence of sufficient plasma glutamine, the body will break down skeletal muscle stores, and gut integrity (gut mucosal barrier function) and immunity will be compromised. Because L-Gln is utilised during exercise, a more recent phenomenon of deficiency has been explored and glutamine depletion has been linked with 'over-training syndrome'.

MAIN ACTIONS

L-Glutamine has many important biological functions within the human body. It is an important fuel for the intestinal mucosal cells, hepatocytes and rapidly proliferating cells of the immune system, assists in the regulation of acid balance, thus preventing acidosis, acts as a nitrogen shuttle protecting the body from high levels of ammonia, and is involved in the synthesis of amino acids (including L-glutamate), gamma aminobutyric acid (GABA), glutathione (an important antioxidant), purine and pyramidine nucleotides, amino acid sugars in glycoproteins and glycans, and nicotinamide adenosine dinucleotide (NAD). It is also involved in protein synthesis and energy production (Boelens et al 2001, Kohlmeier 2003, Miller 1999, Niihara et al 2005, Patel et al 2001, PDRHealth 2006a).

Gastrointestinal protection/repair

According to in vitro and in vivo research, L-Gln aids in the proliferation and repair of intestinal cells (Chun et al 1997, Rhoads et al 1997, Scheppach et al 1996) and is the preferred respiratory fuel for enterocytes (and also utilised by colonocytes) (Miller 1999). It is thus vital for maintaining the integrity of the intestinal lining and preventing the translocation of microbes and endotoxins into the body. In addition, L-Gln helps to maintain secretory IgA, which functions primarily by preventing the attachment of bacteria to mucosal cells (PDRHealth 2006a, Yu et al 1996).

According to evidence from animal studies, it may also assist in preventing atrophy following colostomy (Paulo 2002) and irradiation (Diestel et al 2005), and intestinal injury by inhibiting intestinal cytokine release (Akisu et al 2003). L-glutamine depletion induces apoptosis by triggering intercellular events that lead to cell death (Paquette et al 2005), resulting in altered epithelial barrier competence (increased intestinal permeability), bacterial translocation and increased mortality. Under experimental conditions, L-Gln may assist in maintaining intestinal barrier function by increasing epithelial resistance to apoptotic injury, reducing oxidative damage, attenuating programmed cell death and promoting re-epithelialisation (Masuko 2002, Ropeleski et al 2005, Scheppach et al 1996) and may thus reduce bacterial and endotoxin translocation (Chun et al 1997).

Immunomodulation

L-Glutamine has demonstrated immunomodulatory activity in animal models of infection and trauma, as well as trauma in humans. L-Glutamine acts as the preferred respiratory fuel for lymphocytes, is essential for cell proliferation, and can enhance the function of stimulated immune cells.

Extracellular glutamine concentration affects lymphocyte, IL-2 and interferon-gamma (IFN-gamma) proliferation, cytokine production, phagocytic and secretory macrophage activities and neutrophil bacterial killing (Miller 1999, Newsholme 2001, PDRHealth 2006a). In humans, L-Gln may enhance both phagocytosis and reactive oxygen intermediate production by neutrophils (Furukawa et al 2000) and support the restoration of type-1T-lymphocyte responsiveness following trauma (Boelens et al 2004). In a randomised trial, there was a reduced frequency of pneumonia, sepsis and bacteraemia in patients with multiple traumas who received glutamine-supplemented enteral nutrition (Houdijk et al 1998).

In addition, effects on the gastrointestinal tract may contribute significantly to immune defence by maintaining gut-associated lymphoid tissue and secretory IgA (preventing the attachment of bacteria to the gut mucosa) and maintaining gut integrity (thus preventing the translocation of microbes and their toxins, especially gram-negative bacteria from the large intestine) (Miller 1999, Yu et al 1996).

Antioxidant

As a precursor to glutathione (together with cysteine and glycine), L-Gln can assist in ameliorating the oxidation that occurs during metabolic stress. Glutathione protects epithelial cell membranes from damage, and its depletion can negatively affect gut barrier function and result in severe degeneration of colonic and jejunal epithelial cells (Iantomasi 1994, Ziegler et al 1999). In animal studies, it has also been shown to inhibit fatty acid oxidation, resulting in a reduction in body weight and alleviation of hyperglycaemia and hyperinsulinaemia in mice fed a high-fat diet (Opara et al 1996).

Anabolic/anticatabolic

As L-Gln is stored primarily in skeletal muscles and becomes conditionally essential under conditions of metabolic stress, the anticatabolic/anabolic properties of supplemented L-Gln are likely due to a sparing effect on skeletal muscle stores.

Following strenuous exercise, glutamine levels are depleted by approximately 20%, resulting in immunodepression (Castell 2003, Castell & Newsholme 1997, Rogero et al 2002). As a result supplemental L-Gln may be of benefit in athletes to prevent the deleterious effects of glutamine depletion associated with 'over-training syndrome'. Evidence supporting a direct ergogenic effect is currently lacking.

Cardioprotective

In vitro, L-Gln has been shown to assist in the maintenance of myocardial glutamate, ATP and phosphocreatine, and in the prevention of lactate accumulation (Khogali et al 1998). In addition to its antioxidant properties and effects on hyperglycaemia

and hyperinsulinaemia (Opara et al 1996), this may suggest a possible role as a cardioprotective agent.

CLINICAL USE

Deficiency: prevention and treatment

During periods of increased need, L-glutamine is considered conditionally essential. Glutamine depletion can result in increased intestinal permeability, microbial translocation across the gut barrier, impaired wound healing, sepsis and multiple organ failure (Miller 1999). Experimental studies have proposed a number of benefits for patients with conditions that increase glutamine requirements. The suggested mechanisms include effects on pro-inflammatory cytokine expression, gut integrity, enhanced ability to mount a stress response and improved immune cell function, and studies have shown potential benefit with regard to mortality, length of hospital stay and infection.

To date, the results of studies using glutamine dipeptides in TPN have proven to be very promising in treating patients for whom enteral feeding is impossible. Benefits from studies of enteral glutamine supplementation have tended to be less pronounced, but preliminary trials have demonstrated benefits in some conditions, especially at high doses (e.g. 30 g/day enterally) (Wischmeyer 2003).

Critical care settings

A systematic review found trends to suggest that parenteral and enteral glutamine supplementation may reduce mortality, the development of infection and organ failure in critical illness; however, poor study design and possible publication bias limits what conclusions can be drawn from the current data (Avenell 2006).

Abdominal surgery and trauma

A meta-analysis of nine RCTs involving 373 patients was performed to assess the clinical and economical validity of glutamine dipeptide supplementation to parenteral nutrition (PN) in patients undergoing abdominal surgery. The review concluded that glutamine dipeptide has a positive effect in decreasing postoperative infectious morbidity (odds ratio (OR) = 0.24, P = 0.04), shortening the length of hospital stay (WMD = −3.55, 95% $P < 0.00001$) and improving postoperative cumulative nitrogen balance (WMD = 8.35, P = 0.002). No serious adverse effects were identified (Zheng 2006).

Enteral supplementation has not been shown to be as effective in abdominal trauma. In a recent trial, 120 patients with peritonitis or abdominal trauma were randomised to receive either enteral glutamine (45 g/day for 5 days) in addition to standard care (n = 63) or standard care alone (n = 57). No statistically significant benefits were noted in the treatment group for serum malondialdehyde or glutathione levels, infectious complications, survival rate or duration of hospital stay (Kumar et al 2007).

Trauma

Enteral glutamine has been shown to be protective to the gut in experimental models of shock and thus improve clinical outcomes. In a pilot study, enteral glutamine was administered during active shock resuscitation (0.5 g/kg/day during the first 24 hours) and continued for 10 days through the early post-injury period. The treatment was found to be safe and improved gastrointestinal tolerance (vomiting, nasogastric output, diarrhoea and distension). Intensive care unit (ICU) and hospital length of stay were comparable (McQuiggan et al 2008). In a randomised trial using glutamine-enriched enteral nutrition in patients with multiple traumas, there was a reduction in the incidence of pneumonia, sepsis and bacteraemia (Houdijk et al 1998). Parenteral supplementation of alanyl-glutamine dipeptide may also result in better insulin sensitivity in multiple-trauma patients (Bakalar et al 2006).

Clinical note — Total parenteral nutrition (TPN)

L-Glutamine is not very soluble or stable in solution, especially upon heating for sterilisation. As a result, until recently it was not included in TPN, resulting in compromised glutamine status in patients for whom reduced immune status and increased intestinal permeability could potentially increase the risk of morbid infection and mortality. The more soluble and stable synthetic glutamine dipeptides (L-alanyl-L-glutamine (Ala-Gln) and glycyl-L-glutamine (Gly-Gln)) have now been developed as delivery forms of L-Gln for use in TPN. The dipeptide forms can also be used orally and have demonstrated a potential for greater bioavailability than glutamine alone (Macedo Rogero et al 2004).

Numerous studies have now been conducted using glutamine dipeptides in TPN and have shown benefit in preventing deterioration of gut permeability and preserving mucosal structure (Hall et al 1996, Jiang et al 1999, PDRHealth 2006a, van der Hulst et al 1993). In addition, animal studies suggest that glutamine-enriched TPN may attenuate the suppression of CYP3A and CYP2C usually associated with TPN (Shaw et al 2002).

In a meta-analysis of European and Asian randomised controlled trials (RCTs) in elective surgery patients, 13 studies (pooled n = 355) met inclusion criteria and demonstrated a significant reduction in infectious complication and length of hospital stay (weighted mean difference (WMD) of 3.86 days) (Jiang et al 2004). Conversely, a small study using glutamine (10 g) as part of home parenteral nutrition (HPN) for 6 months did not reveal any significant effects compared to placebo for infective complications (36% versus 55%; P = 0.67), nutritional status, intestinal permeability or quality of life. It should be noted that plasma glutamine concentrations were also not affected in this study (Culkin et al 2008).

Burns

Acute burn injury results in depletion of plasma and muscle glutamine, which contributes to muscle wasting, weight loss and infection. In critical illness, supplementation has been shown to minimise these effects and reduce the rate of mortality and length of stay (Windle 2006). In a double-blind controlled trial, 48 severely burned patients (total burn surface area 30–75%, full thickness burn area 20–58%) were randomised into treatment (n = 25; 0.5 g/kg/day glutamine granules for 14 days with oral or tube feeding) or control group (n = 23; glycine placebo). The results indicated that significantly reduced plasma glutamine and damaged immunological function occurred and supplementation with glutamine granules increased plasma glutamine concentration and reduced the degree of immunosuppression. Glutamine improved immunological function (especially cellular immunity), wound healing and length of hospital stay (46.59 ± 12.98 days versus 55.68 ± 17.36 days, $P < 0.05$) (Peng et al 2006).

According to animal studies, oral glutamine supplementation may reduce bacterial and endotoxin translocation after burns by maintaining secretory IgA in the intestinal mucosa (Yu et al 1996). Systematic reviews and practice guidelines generally support glutamine supplementation in critical illness; however, in large or severe burns or inhalation injury there may be a prolonged critical illness phase (>4 weeks). Further research focussing on enteral and parenteral glutamine supplementation and long-term use is required (Windle 2006).

Infants

Enteral and parenteral glutamine supplementation in preterm infants has been shown to have some beneficial effects on neonatal morbidity and mortality; however, these results are controversial (Korkmaz et al 2007). A Cochrane review, which captured studies published prior to mid-2007, assessed seven randomised controlled trials involving 2365 preterm infants and reported that available data from good quality randomised controlled trials indicates that glutamine supplementation does not confer benefits for preterm infants (Tubman et al 2008).

In a recent trial, which was not included in the review, preterm infants (birth weight ≤ 1500 g) received either enteral glutamine supplementation (n = 36; 300 mg/kg/day adjusted over time according to the current weight) or placebo (n = 33) between 8 and 120 days of life. At the end of the fourth month, the glutamine-supplemented group had significantly higher mean weight, length, head circumference, left upper mid-arm circumference (MAC) and left mid-thigh circumference (MTC) than the control group. The effects appeared to occur in a time-dependent pattern (Korkmaz et al 2007). Another study not captured in the Cochrane review reported that oral supplementation (0.25 mg/kg BW) with glutamine did not improve growth or intestinal permeability [lactulose:mannitol ratio: 0.29 (95% confidence interval (CI): 0.23, 0.35) and 0.26 (95% CI: 0.21, 0.32)] in malnourished Gambian infants (Williams et al 2007). It should be noted, however, that this dose is exceptionally low compared to other trials. The dose, route of administration and length of supplementation require further elucidation in larger scale trials before full assessment can be made.

Experimental data has suggested that by stimulating the rate of recovery of the villi and lipid synthesising enzymes, L-Gln treatments could improve the efficacy of enteral feeding in infants recovering from bowel damage (Ahdieh et al 1998). However, a Cochrane review concluded that there was insufficient data available from randomised controlled trials to determine whether glutamine supplementation confers clinically significant benefits for infants with severe gastrointestinal disease (Grover et al 2007).

Some authors have suggested that early glutamine supplementation may also provide longer term benefits. Enteral glutamine supplementation (300 mg/kg/day) between 3 and 30 days of life has been shown to lower the incidence of atopic dermatitis (OR, 0.13; 95% CI, 0.02–0.97) but not the incidence of bronchial hyperreactivity and infectious diseases (upper respiratory, lower respiratory and gastrointestinal) during the first year of life (van den Berg et al 2007). Longer term benefits for neurodevelopment in such infants have also not been confirmed (van Zwol et al 2008).

Strenuous exercise

Following strenuous exercise, glutamine levels are depleted approximately 20% resulting in immunodepression (Castell 2003, Castell & Newsholme 1997, Rogero et al 2002). The type of training is important to note, however, as although previous reports suggest decreased glutamine concentrations in overtrained athletes, progressive endurance training may lead to steady increases in plasma glutamine levels (Kargotich et al 2007).

The provision of glutamine after exercise has been shown to improve immune status (Castell & Newsholme 1997). In a study of 200 elite runners and rowers given a glutamine or placebo drink immediately after and again 2 hours after strenuous exercise, 151 participants returned questionnaires reporting the incidence of infection over the subsequent 7 days. The percentage of athletes reporting no infections was considerably higher in the glutamine group (81%, n = 72) compared to the placebo group (49%, n = 79, $P < 0.001$) (Castell et al 1996).

During recovery from strenuous exercise, rates of lymphocyte apoptosis, hyperammonaemia and whole-body proteolysis may be affected by glutamine supplementation. In a small study of nine triathletes, glutamine supplementation (4 tablets of 700 mg of hydrolysed whey protein enriched with 175 mg of glutamine dipeptide dissolved in 250 mL water) partially prevented lymphocyte apoptosis induced by exhaustive exercise, possibly by a protective effect on mitochondrial function (Cury-Boaventura et al 2008). Both intermittent and continuous intensity exercises increase ammonia, urate, urea and creatinine in the bloodstream. Chronic glutamine supplementation (100 mg/kg BW) given

immediately before exercise may partially protect against elevated ammonia but not urate, urea or creatinine (Bassini-Cameron et al 2008). The addition of glutamine (300 mg/kg BW) to an oral carbohydrate (1 g/kg/h) and essential amino acid (9.25 g) solution had no effect on post-exercise muscle glycogen resynthesis or muscle protein synthesis, but may suppress a rise in whole-body proteolysis during the later stages of recovery (Wilkinson et al 2006).

Conversely, a trial assessing the possible ergogenic effects of glutamine supplementation (300 mg/kg BW) to improve high-intensity exercise performance in trained males was unable to determine a beneficial effect (Haub et al 1998). Currently, the use of glutamine to enhance exercise performance is speculative at best and the cost of the high doses indicated must be considered. Further large-scale research is required to elucidate any potentially beneficial effects.

Gut repair

Preliminary research on enteral (as well as parenteral) glutamine supplementation suggested promise for the use of glutamine in gut repair by: (i) protecting the intestinal mucosa from damage and promoting repair, thus improving intestinal permeability and reducing subsequent microbial and endotoxin translocation, promoting glutathione and S-IgA, and (ii) improving gut immunity. However, while there is some evidence for the use of glutamine in TPN (Hall et al 1996), clinical evidence using oral supplementation is less convincing. As in vitro data suggests that the colonic mucosa receives its nutrients preferentially from the luminal (not vascular) side (Roediger 1986), it has been suggested that glutamine should be more effective when delivered by the enteral route (Kouznetsova et al 1999). This has yet to be determined in clinical trials.

L-Glutamine enemas, twice daily for 7 days, have been shown to reduce mucosal damage and inflammation in experimental models of colitis in rats (Kaya et al 1999); however, preliminary trials in humans using parenteral glutamine (da Gama Torres et al 2008) and oral supplementation in malnourished preterm infants (Williams et al 2007) have not confirmed benefits for intestinal permeability.

Postoperative administration of TPN supplemented with a combination of glutamine and recombinant human growth hormone (rhGH) in patients following portal hypertension surgery prevented intestinal mucous membrane atrophy and preserved intestinal integrity, although the role of glutamine is unclear (Tang et al 2007). In a 1998 randomised, double-blind, placebo-controlled, 4-week trial of 24 HIV patients with abnormal intestinal permeability using 0, 4 or 8 g/day of glutamine, the authors reported a dose-dependent trend towards improved intestinal permeability and enhanced intestinal absorption with glutamine supplementation and recommended further studies to be carried out with higher doses (e.g. 20 g/day) over a longer study period (Noyer et al 1998). It is difficult to extrapolate the findings of this study to the wider community for the purpose of gut repair as there are factors involved in HIV/AIDS that may increase the biological demand for glutamine. Longer term studies may provide more convincing results; however, it is possible that glutamine only stabilises gut barrier function under certain conditions and more research is required to elucidate these.

Crohn's disease

A 4-week study on 18 children with active Crohn's disease fed a glutamine-enriched polymeric diet (Akobeng et al 2000) was unable to demonstrate benefits. A Cochrane review is currently underway to evaluate the effectiveness of glutamine supplementation for induction of remission in Crohn's disease (Srinivasan & Akobeng 2008).

HIV

L-Glutamine has been shown to improve glutathione levels and significantly increase lean body mass in HIV patients (Patrick 2000); however, not all studies confirm this latter effect (Huffman & Walgren 2003). Combined therapy with arginine and the leucine metabolite beta-hydroxy-beta-methylbutyrate has been shown to reverse lean tissue loss in HIV and cancer patients (Rathmacher et al 2004).

During initial HIV infection, the rapid turnover and proliferation of immune cells increase glutamine requirements and later the repeated episodes of infection, fever and diarrhoea may lead to further depletion. As a result, the doses used in the trial mentioned above (4 g and 8 g) may have been insufficient to meet the increased requirement in such patients (Noyer et al 1998).

Highly active antiretroviral therapy may be associated with diarrhoea and other gastrointestinal side effects. In a prospective, randomised, double-blind crossover study, HIV-infected patients with nelfinavir-associated diarrhoea (for >1 month) received L-Gln (30 g/day) or placebo for 10 days. Glutamine supplementation resulted in a significant reduction in the severity of nelfinavir-associated diarrhoea (Huffman & Walgren 2003). A prospective 12-week trial of 35 HIV-positive men experiencing diarrhoea as a result of nelfinavir or lopinavir/ritonavir therapy was also conducted using probiotics and soluble fibre. When glutamine (30 g/day) was added to the regimen of non-responders at week 4, the response rate improved (Heiser et al 2004).

Cancer prevention

In addition to being the major fuel source for rapidly proliferating intestinal and immune cells, L-Gln is also the main fuel source for many rapidly growing tumours and as a result, tumour growth is associated with a depletion in glutamine and glutathione stores and a depression of NK cell activity (Fahr et al 1994, Miller 1999). The increased intestinal permeability, immune suppression and oxidative damage that may result may further compromise the body's ability to deal with the tumour. While concerns exist, and are supported by in vitro evidence, that glutamine supplementation may feed the tumour, animal studies suggest that glutamine supplementation may assist in decreasing tumour growth by enhancing NK cell activity (Fahr et al

Clinical note — Cancer therapy
Side effects of chemotherapy and radiation therapy can significantly affect the quality of life (QOL) of patients undergoing treatment for cancer. A number of trials have demonstrated the benefits of glutamine supplementation for improving side effects such as oral pain and inflammation, increased gut permeability and reduced lymphocyte count.

1994, Miller 1999). Animal studies have demonstrated that glutamine supplementation prevents the promotion of tumour cells in an implantable breast cancer model (Kaufmann et al 2003). The exact effects in different human tumour cell lines require further elucidation.

Gastrointestinal effects

Adding glutamine to chemotherapy appears to reduce the incidence and severity of oral mucositis, a frequent complication of mucotoxic cancer therapy, which causes significant oral pain, increased infection risk and impaired functioning (Peterson et al 2007). For instance, oral glutamine (30 g/day) appears to reduce the incidence of fluorouracil/leucovorin (FU/LV)-induced mucositis/stomatitis (9% versus 38% in the control group; $P < 0.001$) (Choi et al 2007). Reduced oral pain and inflammation have also been observed in patients receiving radiation and chemotherapy during bone marrow transplantation taking oral glutamine (1 g four times daily) (Miller 1999). In a retrospective study involving 41 patients with stage III lung carcinoma treated with thoracic irradiation, prophylactic supplementation with powdered glutamine (10 g/8 hours) was found to be associated with a 27% lower incidence of grade 2 or 3 acute radiation-induced oesophagitis (ARIE), a 6-day delay in ARIE (22 days versus 16 days), and weight gain during radiotherapy (Topkan et al 2008). In another study, L-Gln (4 g twice daily, swish and swallow) was given to 12 patients receiving doxorubicin, one receiving etoposide, and one receiving ifosfamide, etoposide and carboplatinum from day 1 of chemotherapy for 28 days or for 4 days past the resolution of any post-chemotherapy mucositis. Oral supplementation with glutamine significantly decreased the severity of chemotherapy-induced stomatitis (Skubitz & Anderson 1996). In a small study, parenteral glutamine supplementation was shown to protect the gastrointestinal mucosa against fluorouracil/calcium-folinate (CF) chemotherapy-induced damage (Decker-Baumann et al 1999). Yoshida et al (1998, 2001) have also shown that 30 g/day L-Gln for 28 days attenuates the increased gut permeability and reduced lymphocyte count observed in patients undergoing cisplatin and fluorouracil therapy for oesophageal cancer.

In a small Phase I trial ($n = 15$), glutamine was co-administered in an attempt to escalate the dose of a chemoradiotherapy regimen (weekly paclitaxel and carboplatin with concurrent radiation therapy). The addition was deemed unsuccessful due to multiple severe toxicities including haematological toxicities and oesophagitis (Jazieh et al 2007). The role of glutamine in reducing taxane-associated dysgeusia (taste alteration) appears limited (Strasser et al 2008).

In a double-blind, placebo-controlled, randomised trial, oral glutamine (18 g/day) or placebo was given to 70 chemotherapy naive patients with colorectal cancer 5 days prior to their first cycle of fluorouracil (450 mg/m^2) in association with folinic acid (FA) (100 mg/m^2), which was administered intravenously for 5 days. Glutamine treatment was continued for 15 days and was shown to reduce the negative effects on intestinal absorption and permeability induced by the chemotherapy and to potentially reduce diarrhoea (Daniele et al 2001). L-Glutamine may also reverse the decrease in goblet cells induced by fluorouracil (Tanaka & Takeuchi 2002). A Cochrane review is currently underway to assess whether glutamine supplementation decreases complications in patients with colorectal cancer, and whether glutamine supplementation decreases the length of hospital stay and thereby the costs of treatment (Lemos et al 2008).

Chemotherapy-induced peripheral neuropathy (CIPN)

CIPN is a significant adverse effect associated with neurotoxic chemotherapy (especially taxanes, platinum compounds and vinca alkaloids). In a recent review, two studies were identified that suggested beneficial effects. In one study, oral glutamine was found to be effective in reducing peripheral neuropathy associated with high-dose paclitaxel resulting in a reduction in numbness, dysaesthesias and motor weakness, as well as a smaller loss of vibratory sensation (Amara 2008). Another study found that the addition of oral glutamine (15 g twice daily for seven consecutive days every 2 weeks starting on the day of oxaliplatin infusion) resulted in a significant reduction in the incidence and severity of peripheral neuropathy, less interference with activities of daily living (16.7% versus 40.9%), and less need for oxaliplatin dose reduction due to adverse effects (7.1% versus 27.3%). The addition of Gln did not affect response to chemotherapy or survival (Wang et al 2007).

Other benefits

In one report, L-Gln (10 g three times daily), given 24 h after receiving paclitaxel, appeared to prevent the development of myalgia and arthralgia associated with treatment (PDRHealth 2006a). In children with solid tumours receiving chemotherapy, oral glutamine supplementation (4 g/m^2/day) may improve nutritional and immunological parameters and reduce requirements for antibiotics (Okur et al 2006). Glutamine may also increase tumour methotrexate concentration and tumoricidal activity and reduce side effects and mortality rates (Miller 1999, PDRHealth 2006a).

OTHER USES

Alcoholism

Preliminary studies suggested a potential for glutamine to reduce alcohol cravings; however, these effects have not yet been studied in controlled trials

on humans (PDRHealth 2006a). More recently, in vitro research has suggested that glutamine supplementation may inhibit the deleterious effects of alcohol on the tight junctions of the gut mucosa and in turn reduce the increased risk for gastrointestinal cancers in alcoholics (Basuroy et al 2005, Seth et al 2004).

Acute pancreatitis

The enteral administration of L-Gln (15 mg/kg/day) to rats with acute pancreatitis resulted in a reduction in necrosis and infectious complications by decreasing the bacterial translocation rate (Avsar et al 2001).

Sickle cell disease

Orally administered L-Gln improves the nicotinamide adenosine dinucleotide (NAD) redox potential of sickle red blood cells (RBC). Investigations of blood samples taken from five adult patients with sickle cell anaemia who had been on L-Gln (30 g/day) therapy for at least 4 weeks consistently resulted in improvement of sickle RBC adhesion to human umbilical vein endothelial cells compared to the control group. The authors conclude that these results suggest positive physiological effects for L-Gln in sickle cell disease (Niihara et al 2005).

Other conditions

Glutamine is a popular supplement in naturopathic practice and sometimes used for conditions that may be associated with compromised intestinal permeability such as food allergies, leaky gut syndrome and malabsorption syndromes, including diarrhoea. It may also be used for conditions such as dermatitis and general fatigue, based on the theory that compromised intestinal permeability provides the opportunity for undigested food particles (especially proteins) to enter the systemic circulation and gives rise to an unwanted immune response that manifests as a skin reaction or as lethargy.

DOSAGE RANGE

Naturally occurring food proteins contain 4–8% of their amino acid residues as glutamine and so the daily consumption is usually less than 10 g/day (Hall et al 1996).

Supplemental L-Gln is available for oral and enteral use (in capsules, tablets and powder form) and in a dipeptide form for parenteral use.

While solubility and stability are primarily factors for TPN solutions, several factors should also be considered when using oral supplements, as powder forms are often mixed into a solution to enable easy administration of higher doses: 1 g of L-Gln dissolves in 20.8 mL of water at 30°C (PDRHealth 2006a) and is stable for up to 22 days if stored at 4°C (Hornsby-Lewis et al 1994). Ideally, powdered formulas should be consumed immediately after mixing.

- Gut repair: 7–21 g taken orally as a single dose or in divided doses.
- Cancer therapy: 2–4 g twice daily swished in the mouth and swallowed (up to 30 g have been used in trials and given orally in divided doses).
- Critical illness: 5 g/500 mL of enteral feeding solution.
- HIV: 30 g/day taken orally as a single dose or in divided doses.
- Infection: 12–30.5 g in an enteral feeding solution.
- Infants: 300 mg/kg/day added to breast milk or to preterm formula.

ADVERSE REACTIONS

Toxicity studies in rats fed up to 5% of their diet in L-Gln showed no toxic events (Tsubuku et al 2004) and glutamine dose–response studies have demonstrated 'good tolerance without untoward clinical or biochemical effects' (Ziegler et al 1999). Based on the available published human clinical trial data, glutamine intakes up to 14 g/day appear to be safe in normal healthy adults. Higher levels have been tested without adverse effects and may be safe; however, the data for intakes above 14 g is not sufficient for a confident conclusion of long-term safety (Shao & Hathcock 2008).

Most adverse reactions are mild and uncommon; they include gastrointestinal complaints such as constipation and bloating (PDRHealth 2006a). No evidence of harm has been observed in the studies conducted to date (Wischmeyer 2003).

A report exists of mania in two hypomanic patients after self-medication with up to 4 g/day glutamine (Membane 1984). As glutamine is a precursor of GABA, this may provide a possible explanation.

Two cases of a transient increase in liver enzyme levels have also been reported (Hornsby-Lewis et al 1994).

SIGNIFICANT INTERACTIONS

Radiation and chemotherapy

Benefits have been observed for the use of L-Gln during radiation and chemotherapy (see 'Clinical note — Cancer therapy').

Indomethacin/NSAIDs

Concomitant use of L-Gln (7 g three times daily) and indomethacin may ameliorate the increased intestinal permeability caused by indomethacin. The inclusion of misoprostol may also have a synergistic effect with this combination (Hond et al 1999, PDRHealth 2006a, Tanaka & Takeuchi 2002) — beneficial interaction possible.

Human growth hormone

In patients with severe short bowel syndrome, concomitant use of L-Gln and human growth hormone may enhance nutrient absorption (PDRHealth 2006a).

CONTRAINDICATIONS AND PRECAUTIONS

It is contraindicated in patients with hypersensitivity to glutamine or hepatic disease or any condition where there is a risk of accumulation of nitrogenous wastes in the blood, thus increasing the risk of ammonia-induced encephalopathy and coma.

It should only be used in people with chronic renal failure under professional supervision.

PREGNANCY USE

Safety in pregnancy has not been established; however, doses in line with normal dietary intake (approximately 10 g/day) are unlikely to be cause for concern.

PATIENTS' FAQs

What will this supplement do for me?

L-Glutamine is an amino acid that is used by the immune systems and intestinal cells as a fuel source. People with critical illnesses, stress, burns, injury or having undergone surgery or undertaking strenuous physical exercise require an increased intake to restore glutamine levels to normal and avoid loss of muscle mass and compromised immune function. It also promotes gastrointestinal repair and may improve tolerance to some anticancer treatments.

When will it start to work?

This will depend on the indication for which it is being used.

Are there any safety issues?

Glutamine appears to be a safe supplement; however, it should not be used by people who are hypersensitive to this compound, those with liver disease or any condition where there is a risk of accumulation of nitrogenous wastes in the blood (e.g. Reyes syndrome).

It should be used only by people with chronic renal failure under professional supervision.

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Goji

HISTORICAL NOTE For thousands of years in traditional Chinese medicine, the fruit of the lycium shrub has been used as both a food and an important medicinal substance. In fact, the earliest known Chinese medicinal monograph documented medicinal use of *L. barbarum* around 2300 years ago. According to this tradition, it is believed that the fruit has anti-ageing properties, nourishes the kidneys and liver by tonifying yin deficiency and brightens the eyes. It also has a long history of use as a traditional remedy for male infertility and is included in most fertility-promoting Chinese herbal remedies (Luo et al 2006). In China it is known by several names such as Gou Qi Zi or Gouqizi which probably led to the name it is known as here, goji.

COMMON NAME
Goji

OTHER NAMES
Gou Qi Zi, Gouqizi, Fructus Lycii, Kei Tze, Wolfberry

SCIENTIFIC NAME
Lycium barbarum (Solanaceae family)

PLANT PART USED
Fruit

Goji berry is a deep-red, dried fruit about the same size as a raisin, but with a different taste. The berries have a slight chewy consistency and taste like a mixture of cherries and cranberries without the sweetness of raisins.

CHEMICAL COMPONENTS
The reddish orange colour of the fruit is derived from a group of carotenoids, which make up only 0.03–0.5% of the dried fruit. The predominant carotenoid is zeaxanthin, which comprises about one-third to one-half of the total carotenoids present (Inbaraj et al 2008). The fruit also contains various small molecules, such as betaine, cerebroside, beta-sitosterol, p-coumaric acid, various vitamins (e.g. B1, B2, vitamin C), and minerals (e.g. iron, selenium, zinc). Among these chemical constituents, the most valuable and pharmacologically active components are a group of unique, water-soluble glycoconjugates — collectively termed *Lycium barbarum* polysaccharides (LBPs) — that are estimated to comprise 5–8% of the dried fruit (Amagase et al 2009).

MAIN ACTIONS

Antioxidant
LBPs have a high in vitro antioxidant score (Amagase et al 2009). Goji stimulates endogenous antioxidant mechanisms and has been shown to significantly increase superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px), and reduce lipid peroxidation (indicated by decreased levels of malondialdehyde, MDA) in humans (Amagase et al 2009). A study of streptozocin-induced diabetic animals found that LBP can restore abnormal oxidative indices to near normal levels (Li 2007).

The zeaxanthin component found in whole goji berries is bioavailable in humans (Cheng et al 2005) and is likely to contribute the fruit's in vivo antioxidant effects. Bioavailability of zeaxanthin from freeze-dried wolfberries can be greatly enhanced when consumed in hot skimmed milk compared to hot water or warm milk (Benzie et al 2006).

Antidiabetic
A study by Zhao et al demonstrated that diabetic animals treated with LBP for 3 weeks resulted in a significant decrease in the concentration of plasma triglyceride and weight in non insulin dependent diabetes mellitus (NIDDM) rats. Furthermore, LBP markedly decreased the plasma cholesterol levels, fasting plasma insulin levels and postprandial glucose levels at 30 min during oral glucose tolerance test and significantly increased the Insulin Sensitive Index in NIDDM rats (Zhao et al 2005b). The fruit extract of goji has also shown hypoglycaemic and lipid-lowering activities in diabetic animals whilst not affecting healthy animals (Luo et al 2004). It

appears that the polysaccharides and vitamin antioxidants are responsible for these particular effects.

Neuroprotective

Goji berry extract and LBP display neuroprotective activity in several different experimental models.

An aqueous extract isolated from *L. barbarum* exhibited significant protection on cultured neurons against harmful chemical toxins (A beta and dithiothreitol) by reducing the activity of both caspase-3 and -2, but not caspase-8 and -9 (Yu et al 2007). A new arabinogalactan-protein (LBP-III) was isolated from LBP, which appeared to have the strongest effect.

LBP demonstrates neuroprotective effects in the retina in several experimental models of glaucoma (Chan et al 2007, Chang & So 2008, Yu et al 2007). The polysaccharide-containing extract (LBP) from *L. barbarum* exhibited neuroprotective effects in the retina against ocular hypertension in a laser-induced glaucoma animal model (Yu et al 2007). Chang and So confirmed that LBP protects retinal ganglion cells in vivo (Chang & So 2008).

LBP protects neurons against beta-amyloid peptide toxicity in neuronal cell cultures (Chang & So 2008).

Reduces chemotherapy- and radiotherapy-induced toxicity

LBP elicited a typical cardioprotective effect on doxorubicin (DOX)-related oxidative stress in an experimental model (Xin et al 2007). Furthermore, in vitro cytotoxic study showed the antitumour activity of DOX was not compromised by LBP.

Interestingly, another animal study identified that LBP promotes the peripheral blood recovery of irradiation or chemotherapy-induced myelosuppressive mice (Gong et al 2005). Compared to controls, 50 mg/kg LBP significantly ameliorated the decrease of peripheral white blood cells and peripheral red cells in irradiated myelosuppressive mice. Higher doses significantly enhanced peripheral platelet counts.

Immune modulation

LBPs have been known to have a variety of immunomodulatory functions including activation of T cells, B cells and NK cells (Chen et al 2008, Zhu et al 2007).

A polysaccharide–protein complex isolated from *L. barbarum* (LBP) activated macrophages in vivo (Chen et al 2009). The mechanism may be through activation of transcription factors NF-kappaB and AP-1 to induce TNF-alpha production and up-regulation of major histocompatibility complex (MHC) class II co-stimulatory molecules. LBP also activates T cells.

Sexual behaviour and male reproductive function

Studies with experimental models suggest the polysaccharides in goji berries may improve sexual behaviour and reproductive function (Luo et al 2006). LBP improved the copulatory performance and reproductive function of hemicastrated male rats, such as shortened penis erection latency and mount latency, regulated secretion of sexual hormones and increased hormone levels, raised accessory sexual organ weights, and improved sperm quantity and quality (Luo et al 2006).

Studies with LBP indicate a protective effect on testicular cells against a variety of insults. Luo et al (2006) demonstrated a dose-dependent protective effect for LBP against DNA oxidative damage of mouse testicular cells in vivo. LBP also inhibits time- and hyperthermia-induced structural damage in murine seminiferous epithelium, in vitro (Wang et al 2002). Moreover, LBP delays apoptosis in this system, both at normothermic and hyperthermic culture conditions. Considering the oxidative stress is suspected to be a major cause of structural degradation and apoptosis in hyperthermic testes, the protective effect of LBP may be mediated by an antioxidant mechanism of action.

OTHER ACTIONS

One of *L. barbarum* glycoconjugates promoted the survival of human fibroblasts cultured in suboptimal conditions and demonstrated important skin-protective properties (Zhao et al 2005a).

CLINICAL USE

Goji has become more popular for the last few years due to its public acceptance as a 'super food' with highly advantageous nutritive and antioxidant properties. It is touted as being able to improve wellbeing and protect against cancer and other serious diseases. Most investigation with goji has been conducted in China and there is little clinical research information available in English language journals.

Improved wellbeing

A randomised, double-blind, placebo-controlled clinical trial examined the general effects of orally consumed goji berry, *L. barbarum*, as a standardised juice (GoChi; FreeLife International LLC, Phoenix, AZ) to healthy adults for 14 days (Amagase & Nance 2008). The study was designed to measure multiple outcomes based on the traditionally understood properties of the product. Comparisons between day 1 and day 15 revealed that goji treatment significantly increased ratings for energy level, athletic performance, quality of sleep, ease of awakening, ability to focus on activities, mental acuity, calmness, and subjective feelings of general wellbeing. Furthermore, goji significantly reduced fatigue and stress, and improved regularity of gastrointestinal function. In contrast, the placebo group ($n = 18$) showed only two significant changes, heartburn and elevated mood.

Aphrodisiac and increased male fertility

Traditional evidence and animal studies provide some support for its use; however, well-controlled clinical studies are not available to determine the effectiveness of goji in this capacity.

OTHER USES

Goji is broadly marketed as a 'super food' with significant health-promoting qualities. The high concentration of antioxidants, vitamins and minerals in

the fruit makes it a nutritious substance; however, claims that it cures major diseases are not founded on sound clinical evidence.

The high concentration of zeaxanthin in the berries makes it a good dietary source of this carotenoid. As such, indications which respond to increased zeaxanthin intake may also respond to an equivalent dose from goji berries. (See Lutein/zeaxanthin monograph for further information.)

DOSAGE RANGE

Daily dose: 6–15 g daily.

ADVERSE REACTIONS

Not known.

SIGNIFICANT INTERACTIONS

Warfarin

Two case reports exist in the literature, suggesting an interaction between warfarin and goji is possible. One case was of an 80-year-old Chinese woman on a chronic stable dose of warfarin, who experienced two episodes of an elevated international normalised ratio (INR) after drinking herbal tea containing goji (Leung et al 2008). Another case describes a 61-year-old Chinese woman, previously stabilised on anticoagulation therapy (INR 2–3) who had an elevated INR of 4.1 as a result of drinking a concentrated Chinese herbal tea made from *L. barbarum* L. fruits (3–4 glasses daily). No changes in her other medications, lifestyle or dietary habits were revealed (Lam et al 2001). Until confirmation from controlled trials is available, caution is advised.

CONTRAINDICATIONS AND PRECAUTIONS

None known.

PREGNANCY USE/PATIENT COUNSELLING

The fruit is likely to be safe when taken in typical dietary doses; however, the safety of higher doses is unknown.

PATIENTS' FAQs

What will this herb do for me?

Goji fruits are a nutritious source of vitamins, minerals and antioxidants. Preliminary tests show that it has multiple health-promoting effects, but little human research is available to confirm activity.

When will it start to work?

As a concentrated source of nutrients, general benefits will start within several days.

Are there any safety issues?

Two case reports suggest a possible interaction between warfarin and goji berry, but this remains to be confirmed.

PRACTICE POINTS/PATIENT COUNSELLING

- Goji berries are a nutritious source of antioxidants, vitamins and minerals.
- The LBPs in the fruit that are considered to be the most important for pharmacological activity are attracting research interest.
- Preliminary studies in test tubes and with animal models indicate the berry and/or polysaccharides enhance immune function, exert neuroprotective effects, reduce lipid and blood glucose levels in diabetic models and improve male fertility; however, human tests are not available to determine whether these effects are significant in humans.
- Use with caution in people taking warfarin.

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Goldenrod

HISTORICAL NOTE Goldenrod has been used therapeutically for centuries for bladder conditions and wound healing. The name *Solidago* is from the Latin verb 'to make whole'. In 1934, reports from the US Department of Agriculture suggested that goldenrod was considered as a potential future source of commercially prepared rubber, although it was noted that domestication of the plant would be difficult as it is vulnerable to fungal infection and insect attack.

COMMON NAME
Goldenrod

OTHER NAMES
Aaron's rod, blue mountain tea, sweet goldenrod, woundwort

BOTANICAL NAME/FAMILY
Solidago canadensis (Canadian goldenrod), *Solidago virgaurea* (European goldenrod) (family Asteraceae [Compositae]). There are numerous species of goldenrod.

PLANT PARTS USED
Dried aerial parts — flowers and leaves.

CHEMICAL COMPONENTS
Flavonoids, including rutin, catechol tannins, triterpene saponins, phenol glycosides, phenolic acids, one essential oil, diterpene lactones and polysaccharides.

MAIN ACTIONS
The pharmacology of goldenrod has not been significantly investigated; therefore, evidence of activity derives from traditional, in vitro and animal studies.

Diuretic
Goldenrod is considered an aquaretic medicine, as it promotes fluid loss without an associated disruption to electrolytes. Two animal studies have confirmed diuretic activity (Chodera et al 1991, Leuschner 1995). According to one study, excretion of calcium increases whereas excretion of potassium and sodium decreases (Chodera et al 1991). A review of herbal medicines for the urinary tract concluded that goldenrod is a major diuretic herb (Yarnell 2002).

Antispasmodic and anti-inflammatory
High doses of a commercial preparation of *S. gigantea* extract have demonstrated anti-inflammatory activity in an animal model, comparable to those of the pharmaceutical anti-inflammatory medicine diclofenac (Leuschner 1995). Other tests with an extract of *S. virgaurea* have also produced similar results (el Ghazaly et al 1992).

The herbal combination consisting of *Populus tremula*, *S. virgaurea* and *Fraxinus excelsior* has demonstrated dose-dependent anti-inflammatory, analgesic and antipyretic effects comparable to those of NSAIDs in several animal models (Okpanyi et al 1989). Although encouraging, the role of *Solidago* in this study is uncertain.

OTHER ACTIONS
Traditionally believed to have an effect on the micro-architecture of the kidney.

Antifungal
Inhibitory effects on human pathogenic yeasts such as *Candida* and *Cryptococcus* spp have been demonstrated for triterpenoid glycosides isolated from *S. virgaurea* (Bader et al 1990).

Antibacterial
A moderate antibacterial activity in vitro against certain strains of bacteria, including species of *Bacillus*, *Proteus* and *Staphylococcus* has been demonstrated from an extract of *S. virgaurea* (Thiem & Goslinska 2002).

Anticancer effects
An extract of *S. virgaurea* has demonstrated antineoplastic activity in vitro using a variety of cell lines, including prostate, breast, small cell lung carcinoma and melanoma, and in vivo in a mouse model of prostate cancer (Gross et al 2002).

CLINICAL USE
Goldenrod has not been significantly investigated under controlled study conditions, so most evidence is derived from traditional use, in vitro and animal studies.

Cystitis
The most common use of goldenrod is in the treatment of bladder infections. Both the Commission E (Blumenthal et al 1998) and ESCOP (2003) have approved its use for irrigation of the urinary tract, with ESCOP also indicating usefulness as adjunctive treatment for bacterial urinary tract infections (UTIs).

Arthritis (in combination)
The product Phytodolor contains alcoholic extracts of *Populus tremula*, *Fraxinus excelsior* and *S. virgaurea* and is standardised to 0.14 mg/mL of isofraxidine, 1 mg/mL salicine and 0.07 mg/mL of total flavonoids. As part of this combination, goldenrod has been investigated in patients with rheumatoid arthritis (RA), osteoarthritis and back pain. Pain was significantly reduced by treatment with Phytodolor in a placebo-controlled study of 47 patients (Weiner & Ernst 2004). Symptom relief was equally effective amongst patients receiving half-strength, normal (60 drops three times daily) or double-strength treatment. A shorter placebo-controlled study of 2 weeks duration found that Phytodolor reduced the

need for conventional drug doses in subjects with 'at least one rheumatological diagnosis' (Weiner & Ernst 2004). Similarly, Phytodolor reduced requirements of diclofenac compared to placebo in a smaller study of 30 patients (Weiner & Ernst 2004). A 2-week placebo-controlled study of 30 subjects with osteoarthritis demonstrated that treatment with Phytodolor significantly reduced pain and improved grip strength (Weiner & Ernst 2004). A recent review found that Phytodolor may be a suitable alternative to NSAIDs and COX2 inhibitors for the treatment of rheumatic disease (Gundermann & Muller 2007). The role of goldenrod in achieving these results is unclear.

Inflammation of the nasopharynx with catarrh

Goldenrod is also used to relieve symptoms in this condition. The astringent activity of the tannin components provides a theoretical basis for its use.

OTHER USES

In many countries, goldenrod is used to prevent urolithiasis and eliminate renal calculi (Skidmore-Roth 2001). It is also used in children with otitis media and nasal catarrh.

Traditional uses

Goldenrod is used both internally and externally for a variety of conditions. Internally it is used to treat upper respiratory tract catarrh, arthritis, menorrhagia and urological complaints, vomiting and dyspepsia, and externally it is used to support wound healing and as a mouth rinse for inflammatory conditions of the mouth and gums.

DOSAGE RANGE

- Infusion of dried herb: 0.5–2 g in 150 mL of boiled water for at least 10 minutes.
- Fluid extract (1:1) (g/mL): 0.5–2 mL taken 2–4 times daily between meals.

ADVERSE REACTIONS

Handling the plant has been associated with allergic reactions ranging from allergic rhinoconjunctivitis and asthma to urticaria. There is one study of a cohort predominantly comprising florists who had presented with complaints relating to the handling of plants which found the extensive cross-sensitisation to pollen of several members of the Asteraceae family (e.g. *Matricaria*, *Chrysanthemum* and *Solidago*) and to pollen of the Amaryllidaceae family (*Alstroemeria* and *Narcissus*) (de Jong et al 1998).

SIGNIFICANT INTERACTIONS

None known

CONTRAINDICATIONS AND PRECAUTIONS

Commission E cautions against use as irrigation therapy when heart or kidney disease is also present (Blumenthal et al 1998).

People with known allergy to goldenrod or who are allergic to the Asteraceae (Compositae) family of plants should avoid this herb.

PREGNANCY USE

From limited use in pregnant women, it appears that no increase in frequency of malformation or other harmful effects have been reported, although animal studies are lacking (Mills & Bone 2005).

PRACTICE POINTS/PATIENT COUNSELLING

- Goldenrod has a long history of use, but has not been tested in humans to any significant extent.
- Traditionally, it has been used internally to reduce upper respiratory catarrh, arthritis, menorrhagia, urological complaints and dyspepsia, and externally to promote wound healing and as a mouth rinse for inflammatory conditions of the mouth and gums.
- In Europe, goldenrod is a popular herb for treating lower UTIs and preventing kidney stones.
- When used as part of the commercial preparation, Phytodolor, it provides effective symptom relief in RA and osteoarthritis according to several clinical studies.
- It is considered an aquaretic herb, which induces diuresis but not potassium and sodium loss.
- Preliminary studies in animal models suggest anti-inflammatory activity comparable to that of NSAIDs, but human studies are not available to confirm the clinical significance of these findings.

PATIENTS' FAQs

What will this herb do for me?

Goldenrod has diuretic and anti-inflammatory activity, which may be useful in cases of bladder inflammation, although clinical testing has not yet been conducted to confirm this.

When will it start to work?

This is unknown.

Are there any safety issues?

People who are allergic to goldenrod or the Asteraceae family of plants should avoid taking this herb.

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Goldenseal

HISTORICAL NOTE Goldenseal is indigenous to North America and was traditionally used by the Cherokees and then by early American pioneers. Preparations of the root and rhizome were used for gastritis, diarrhoea, vaginitis, dropsy, menstrual abnormalities, eye and mouth inflammation and general ulceration. In addition to this, the plant was used for dyeing fabric and weapons. Practitioners of the eclectic school created a high demand for goldenseal around 1847. This ensured the herb's ongoing popularity in Western herbal medicine, but unfortunately led to it being named a threatened species in 1997. Today, most high-quality goldenseal is from cultivated sources.

COMMON NAME
Goldenseal

OTHER NAMES
Eye root, jaundice root, orange root, yellow root.

BOTANICAL NAME/FAMILY
Hydrastis canadensis (family Ranunculaceae)

PLANT PARTS USED
Root and rhizome

CHEMICAL COMPONENTS
Isoquinoline alkaloids, including hydrastine (1.5–5%), berberine (0.5–6%) and canadine (tetrahydroberberine, 0.5–1.0%). Other related alkaloids include canadaline, hydrastidine, corypalmine and isohydrastidine.

MAIN ACTIONS
A wealth of empirical data exists for the medicinal use of goldenseal; however, much of the research has been conducted using the chief constituent berberine. It is recommended that goldenseal products be standardised to contain at least 8 mg/mL of berberine and 8 mg/mL of hydrastine (Bone 2003).

Antimicrobial
In vitro testing has demonstrated antibacterial activity of both the whole extract of goldenseal and the major isolated alkaloids (berberine, beta-hydrastine, canadine and canadaline) against *Staphylococcus aureus*, *Streptococcus sanguis*, *Escherichia coli* and *Pseudomonas aeruginosa* (Scazzocchio et al 2001). In a study, two flavonoids isolated from goldenseal were shown to exhibit antibacterial activity against the oral pathogens *Streptococcus mutans* and *Fusobacterium nucleatum* (Hwang et al 2003). An added antimicrobial effect against *S. mutans* was noted with the addition of berberine.

Clinical note — Isoquinoline alkaloids
Isoquinoline alkaloids are derived from phenylalanine or tyrosine and are most frequently found in the Ranunculaceae, Berberidaceae and Papaveraceae families (Pengelly 2004). This is a very large class of medicinally active compounds that include the morphinane alkaloids (morphine, thebaine and codeine), the ipecac alkaloids (emetine and cephaeline), the atropine alkaloid (boldine) and the protoberberines (berberine and hydrastine). Many other plants contain berberine, including *Berberis vulgaris* (barberry), *Mahonia aquifolium*/*Berberis aquifolium* (Oregon mountain grape), *Berberis aristata* (Indian barberry), *Coptis chinensis* (Chinese goldthread), *Coptis japonica* (Japanese goldthread) and *Thalictrum minus*.

The methanolic extract of the rhizome inhibited the growth of 15 strains of *Helicobacter pylori* in vitro (Mahady et al 2003). The authors identified berberine and beta-hydrastine as the main active constituents.

Berberine alone, and in combination with both ampicillin and oxacillin, has demonstrated strong antibacterial activity against all strains of methicillin resistant *Staphylococcus aureus* (MRSA) in vitro (Yu et al 2005); 90% inhibition was demonstrated with 64 microgram/mL or less of berberine. Berberine was also found to enhance the effectiveness of ampicillin and oxacillin against MRSA in vitro.

Many of the *Berberis* spp contain the flavonolignan 5′-methoxyhydnocarpin, which inhibits the expression of the multidrug-resistant efflux pumps (Musumeci et al 2003; Stermitz et al 2000a, 2000b); however, it is unknown whether goldenseal contains this compound.

Berberine inhibits the adherence of streptococci to host cells by aiding the release of an adhesin

lipoteichoic acid (an acid that is responsible for the adhesion of the bacteria to the host tissue) from the streptococcal cell surface (Sun et al 1998). Berberine is also able to dissolve lipoteichoic acid–fibronectin complexes once they have been formed. Berberine displays well-defined antimicrobial properties against certain bacteria and such data suggest that it may also be able to prevent adherence and destroy already-formed complexes.

Berberine may also possess antifungal and antiviral properties. Berberine was shown to destroy cell wall and sterol biosynthesis in *Candida* spp. in vitro (Park et al 1999). A study demonstrated the antiviral activity of berberine to be as effective as the DNA polymerase inhibitor ganciclovir in human cytomegalovirus (Hayashi et al 2007). It appeared to work via a different mechanism and may prove useful if used in conjunction to prevent tolerance and reduce toxicity.

Antidiarrhoeal

Berberine decreases intestinal activity by activating alpha-2-adrenoceptors and reducing cyclic adenosine monophosphate (cAMP) (Hui et al 1991). Berberine also inhibits intestinal ion secretion and inhibits toxin formation from microbes (Birdsall & Kelly 1997).

Berberine has demonstrated efficacy in vitro for many bacteria that cause infective diarrhoea, including *E. coli*, *Shigella dysenteriae*, *Salmonella paratyphi*, *Clostridium perfringens* and *Bacillus subtilis* (Mahady & Chadwick 2001). It has also demonstrated activity in vitro against parasites that cause diarrhoea, including *Entamoeba histolytica*, *Giardia lamblia* and *Trichomonas vaginalis*.

The effects of berberine on cholera toxin-induced water and electrolyte secretion were investigated in an experimental in vivo model (Swabb et al 1981). Secretions of water, sodium and chlorine were reduced 60–80 min after exposure to berberine.

Berberine did not alter ileal water or electrolyte transport in the control model. It produced a significant reduction in fluid accumulation caused by infection with *E. coli* in vivo (Khin-Maung & Nwe Nwe 1992). Oral doses of berberine before the toxin was introduced and intragastric injection after infection were both effective. Berberine was shown to inhibit by approximately 70% the secretory effects of *Vibrio cholerae* and *E. coli* in a rabbit ligated intestinal loop model (Sack & Froehlich 1982). As in the other study, the drug was effective when given either before or after enterotoxin binding. In an investigation using pig jejunum, berberine demonstrated a reduction in water and electrolyte secretion after intraluminal perfusion with *E. coli* (Zhu & Ahrens 1982).

Berberine significantly slowed small intestine transit time in an experimental in vivo model (Eaker & Sninsky 1989). Berberine inhibited myoelectric activity, which appears to be partially mediated by opioid and alpha-adrenergic receptors. The antidiarrhoeal properties of berberine may be partially due to the constituents' ability to delay small intestinal transit time.

Cardiovascular actions

Berberine may be effective for congestive heart failure and arrhythmia, as it has demonstrated positive inotropic, negative chronotropic, antiarrhythmic and vasodilator properties (Lau et al 2001).

After 8 weeks of treatment, oral doses of berberine (10 mg/kg) improved cardiac function and prevented development of left ventricular hypertrophy induced by pressure overload in rats (Hong et al 2002, 2003). Berberine was found to reduce left ventricular end-diastolic pressure, improve contraction and relaxation and decrease the amount of the atrophied heart muscle.

Berberine has also been found to increase cardiac output in dogs with left ventricular failure due to ischaemia (Huang et al 1992). Over 10 days, intravenous administration of berberine (1 mg/kg, within 3 min) followed by a constant infusion (0.2 mg/kg/min, 30 min) increased the cardiac output and decreased left ventricular end-diastolic pressure, diastolic blood pressure (DBP) and systemic vascular resistance, but did not affect heart rate. This study shows that berberine may be able to improve impaired left ventricular function by exerting positive inotropic effects and mild systemic vasodilatation. These results, although interesting, should be evaluated cautiously as the method of administration was intravenous. The hypotensive effects of the berberine derivative, 6-protoberberine (PTB-6), were studied in spontaneously hypertensive rats (Liu et al 1999). PTB-6 lowered systolic blood pressure (SBP) in a dose-dependent manner (5 mg/kg: -31.1 ± 1.6 mmHg; 10 mg/kg: -42.4 ± 3.1 mmHg). The berberine derivative also reduced cardiac output and heart rate. The authors conclude that the antihypertensive effect of PTB-6 is probably caused by a central sympatholytic effect.

Hypocholesterolaemic/anti-atherogenic

Berberine upregulates the LDL receptor (LDLR) by stabilising the LDLR mRNA (Abidi et al 2005, Kong et al 2004). A follow-up study confirmed this and went on to demonstrate that the whole root preparation of goldenseal was more effective in up-regulating liver LDLR expression and reducing plasma cholesterol and LDL cholesterol in hyperlipidaemic hamsters than the pure berberine compound (Abidi et al 2006). The authors also noted that canadine effectively upregulated LDLR expression and unlike berberine was not affected by MDR1-mediated efflux from liver cells. In another study, hamsters fed a high-fat diet for 2 weeks, followed by treatment with oral doses of berberine (100 mg/kg) for 10 days, demonstrated a 40% reduction of cholesterol, including a 42% reduction in LDL cholesterol (Kong et al 2004). No effect on HDL cholesterol was noted.

Despite these positive results, a current study found that berberine alone did not lower cholesterol but when combined with plant sterols significantly reduced both total cholesterol and non-HDL cholesterol (Jia et al in press). Rats being fed a high-sucrose, high-fat diet were given berberine (100 mg/kg), plant sterols (1% of total diet), a combination of both or a control mixture for 6 weeks. Whilst

berberine on its own made no appreciable difference, the combination reduced total cholesterol by 41% and non-HDL cholesterol by 59%. Berberine also reduced plasma triglycerides by 31%, which was of marginal statistical significance ($P = 0.054$).

Berberine may have potential as an anti-atherosclerotic agent because of a demonstrated inhibition of lysophosphatidylcholine (lysoPC)-induced DNA synthesis and cell proliferation in vascular smooth muscle cells (VSMCs) in vivo (Cho et al 2005). Berberine also inhibited the migration of lysoPC-stimulated VSMCs and the activity of extracellular signal-regulated kinases, reduced transcription factor AP-1 and intracellular reactive oxygen species. This suggests that berberine may be useful for the prevention of atherosclerosis.

Antidiabetic

A glucose-lowering effect similar to metformin was observed in vitro for berberine; however, no effect was seen on insulin secretion (Yin et al 2002).

Blood glucose, blood lipids, muscle triglycerides and insulin sensitivity were measured before and after the ingestion of berberine or metformin in rats fed a high-fat diet (Gao et al 1997). In this trial, berberine and metformin improved insulin resistance and liver glycogen levels, but had no effect on blood glucose, insulin, lipid and muscle triglyceride levels. The study was able to demonstrate that berberine was as effective as metformin for improving insulin sensitivity in the rats.

Similarly, fasting blood glucose, total cholesterol and triglyceride levels significantly decreased after 8 weeks of treatment with 187.5 or 562.5 mg/kg of berberine in an experimental model of glucose intolerance (Leng et al 2004). An additional in vitro study using insulin secreted from pancreatic cells, incubated with berberine for 12 h, concluded that berberine increased insulin production. The relationship of these trials to oral doses in humans is unknown. In another in vivo test, diabetic rats were treated with berberine (100 or 200 mg/kg) via intragastric means for 21 days (Tang et al 2006). The researchers found that berberine demonstrated hypoglycaemic, hypolipidaemic and antioxidant effects.

Berberine inhibits alpha-glucosidase and therefore reduces the transport of glucose through the intestinal epithelium (Pan et al 2003). Berberine also appears to stimulate glucose uptake through the AMP-AMPK-p38 MAPK pathway, which may be at least partly responsible for its hypoglycaemic effects (Cheng et al 2006).

Berberine may be able to attenuate the renal complications of diabetes. Streptozotocin-induced diabetic rats were fed berberine (200 mg/kg) for 12 weeks in order to examine the effects on kidney function (Liu et al 2008). The results showed significant reductions in fasting blood glucose, blood urea nitrogen, protein and creatinine over 24 h as compared to control animals.

Anti-inflammatory

Berberine inhibits cyclo-oxygenase 2 (COX-2) transcriptional activity (Fukuda et al 1999, Kuo et al 2005) and reduces prostaglandin (PG) synthesis in vitro and in vivo (Kuo et al 2004). Berberine also inhibits kappa B-alpha phosphorylation and degradation, therefore reducing certain inflammatory mediators such as induced tumour necrosis factor (TNF)-alpha and interleukin (IL)-1beta productions in human lung cells (Lee et al 2007). The compound has also been found to reduce proliferation of human lymphocytes in vitro by inhibiting DNA synthesis in activated cells (Ckless et al 1995).

Immune activity

Intragastric administration of the crude extract of goldenseal for 6 weeks increased the production of IgM in vivo (Rehman et al 1999). Berberine has also been found to induce IL-12 p40, a large subunit of IL-12, through the activation of p38 mitogen-activated protein kinase in mouse macrophages (Kang et al 2002). Interleukin-12 is crucial for the development of the Th1 immune response and thus may also have a therapeutic effect in reducing Th2 allergic disorders. A follow-up study demonstrated that pretreatment with berberine induced IL-12 production in stimulated macrophages and dendritic cells (Kim et al 2003). Macrophages pretreated with berberine had an increased ability to induce interferon (IFN)-gamma and a reduced ability to induce IL-4 in antigen-primed $CD4^+$ T-cells. Increased levels of IL-12 appear to deviate $CD4^+$ T-cells from the Th2 to the Th1 pathway. This inhibition of type 2 cytokine responses indicates that berberine may be an effective anti-allergic compound.

The immunosuppressive effects of berberine were investigated in an induced autoimmune model in vivo (Marinova et al 2000). Berberine was administered daily (10 mg/kg) for 3 days before intravenous induction of tubulo-interstitial nephritis (TIN).

Significantly less damage and an increase in renal function were demonstrated in the animals pretreated with berberine as compared to controls after 2 months. Berberine decreased CD3, CD4 and CD8 lymphocytes in comparison with the non-treated animals. These results suggest that berberine may exert an immunosuppressive effect in a TIN model. Clinical trials in human kidney autoimmune diseases are warranted.

Anticancer

Berberine has demonstrated cytotoxic activity in vitro against many strains of human cancer cells (Hwang et al 2006, Kettmann et al 2004, Kuo et al 2005, Meeran et al 2008, Piyanuch et al 2007, Serafim et al 2008, Wang et al in press). This is due in part to the reduction of COX-2 enzymes (Kuo et al 2005, Tai & Luo 2003), damage to the cytoplasmic membrane and DNA fragmentation (Letasiova et al 2005).

The antitumour effects of berberine were investigated on malignant brain tumours in an in vitro and in vivo model (Zhang et al 1990). Berberine (150 mg/mL) demonstrated an ability to kill 91% of cells in six human malignant brain tumour cell lines and 10 mg/kg exhibited an 80.9% cell-kill rate against solid brain tumours in vivo. The addition of

berberine to 1,3-bis(2-chloroethyl)-1-nitrosourea increased cytotoxicity.

Neuroprotective

An in vivo study was designed to investigate the neuroprotective effects of berberine in ischaemic brain injury (Zhou et al in press). Berberine (20 mg/kg) was intragastrically administered 30 minutes before and 1 day after middle cerebral artery occlusion (MCAO) was performed. After 48 hours, infarct size and neurological deficits were significantly reduced in the treatment group as compared to control. The authors were interested in discovering the mechanisms of action and designed a follow-up in vitro study. They found that berberine inhibited reactive oxygen species and protected PC12 cells against glucose and oxygen deprivation.

Berberine may also be effective in Alzheimer's disease according to early in vitro data (Asai et al 2007). Berberine significantly reduced extracellular amyloid-beta peptide levels by modulating amyloid precursor proteins in human neuroglioma H4 cells.

Antidepressant

Oral doses of berberine (10 and 20 mg/kg) were shown to possess antidepressant effects in both the forced swim and tail suspension tests (Peng et al 2007). It was found to be slightly weaker than the positive control desipramine, a tricyclic antidepressant. In the forced swim test, however, berberine was shown to have additive benefits when used with desipramine, fluoxetine (a selective 5-HT reuptake inhibitor) and moclobemide (a monoamine oxidase inhibitor). The authors also noted that noradrenaline and serotonin levels were increased in the frontal cortex and hippocampus of animals in the berberine group (20 mg/kg).

Another in vivo study used the same models and gave animals either 5, 10 or 20 mg/kg of berberine i.p. (Kulkarni & Dhir 2008). They also found that animals in the berberine group demonstrated a reduced immobility period. Berberine (5 mg/kg, i.p.) also improved the efficacy of subeffective doses of standard antidepressant medications in the forced swim test. The acute administration of berberine (5 mg/kg, i.p.) increased noradrenaline (31%), serotonin (47%) and dopamine (31%) in the brain. The authors add that the mechanism may at least in part involve the nitric oxide pathway and/or sigma receptors.

OTHER ACTIONS

Anticatarrhal, astringent, bitter, choleretic, depurative, mucus membrane tonic, vulnerary and oxytocic.

CLINICAL USE

Goldenseal has not been significantly investigated under clinical trial conditions, so evidence is derived from traditional, in vitro and animal studies. Many of these have been conducted on the primary alkaloids. All results are for the isolated compound berberine, and although this compound appears to have various demonstrable therapeutic effects, extrapolation of these results to crude extracts of goldenseal is premature. It should also be noted that equivalent doses of the whole extract of goldenseal are exceptionally high.

Diarrhoea

A double-blind, placebo-controlled, randomised trial examined the effect of berberine alone (100 mg four times daily) and in combination with tetracycline for acute watery diarrhoea in 400 patients (Khin-Maung et al 1985). Patients were divided into four groups and given tetracycline, tetracycline plus berberine, berberine or placebo; 185 patients tested positive for cholera and those in the tetracycline and tetracycline plus berberine groups achieved a significant reduction in diarrhoea after 16 hours and up to 24 hours. The group given berberine alone showed a significant reduction in diarrhoea volume (1 L) and a 77% reduction in cAMP in stools. Noticeably, fewer patients in the tetracycline and tetracycline plus berberine groups excreted vibrios in their stool after 24 hours and interestingly no statistically significant improvements for patients with non-cholera diarrhoea in the tetracycline or berberine group were shown. A later randomised, double-blind clinical trial compared 200 mg of berberine four times daily plus tetracycline, with tetracycline alone in 74 patients with diarrhoea resulting from *V. cholerae* (Khin-Maung et al 1987). There were no statistically significant differences between the two groups.

A randomised controlled trial (RCT) evaluated the effect of berberine sulfate in 165 men with *E. coli*- or *V. cholerae*-induced diarrhoea as compared to tetracycline (Rabbani et al 1987). Patients with *E. coli* were given a single 400 mg dose and those with *V. cholerae* were given either a single 400 mg dose or 1200 mg (400 mg every 8 hours), combined with tetracycline. Berberine reduced mean stool volumes by 48% in the *E. coli* group as compared to control over 24 hours. Patients in the *V. cholerae* group who received 400 mg of berberine as a single dose also had a reduction in stool volume after 16 hours as compared to placebo. The combination of berberine and tetracycline did not show any statistical improvement over tetracycline alone in the *V. cholerae* group.

A follow-up randomised, placebo-controlled trial was designed to evaluate the antisecretory and antimicrobial potential of various antidiarrhoeal agents including berberine in patients with active diarrhoea due to *Vibrio cholerae* or enterotoxic *E. coli* (Rabbani 1996). Berberine at a lower dose of 200 mg resulted in a reduction in stool volume of between 30% and 50% without significant side effects. Berberine was again shown to be more effective in the treatment of diarrhoea resulting from *E. coli* than in cholera.

Berberine may also be effective in the treatment of giardiasis. A comparison-controlled study of 359 children aged between 4 months and 14 years compared berberine (10 mg/kg/day) with metronidazole (20 mg/kg/day) for up to 10 days (Gupte 1975). Negative stool samples were evident in 90% of children receiving berberine after 10 days with

83% remaining negative after 1 month's duration. The results were comparative with the metronidazole (Flagyl) group (95% after 10 days and 90% after 1 month), without side effects. In a similar study, 40 children aged 1–10 years with giardiasis were given berberine (5 mg/kg/day), metronidazole (10 mg/kg/day) or placebo (vitamin B syrup) for 6 days (Choudry et al 1972). In the berberine group, 48% of children were symptom-free after 6 days and 68% had no giardia cysts on stool analysis as compared to the metronidazole group who experienced a 33% reduction in symptoms and a 100% clearance rate for cysts. These results show that berberine may be more effective than Flagyl for symptom relief, but not as effective for clearing the organism from the gastrointestinal tract. The aforementioned study (Gupte 1975) used a higher dose of berberine (10 mg/kg/day), which produced better results; however, the equivalent amount of goldenseal for either dose would be exceedingly high based on an average berberine content of 5%, which would be inappropriate.

Small intestinal transit time was evaluated in 30 healthy subjects in a controlled study (Yuan et al 1994). Transit time was significantly delayed from 71.10 ± 22.04 min to 98.25 ± 29.03 min after oral administration of 1.2 g of berberine. These results suggest that the antidiarrhoeal effect of berberine might be partially due to its ability to delay small intestinal transit time.

Eye infection

A controlled clinical trial of 51 patients with ocular trachoma infections investigated the effectiveness of berberine over 3 weeks with a 1-year follow-up (Babbar et al 1982). Subjects who used the 0.2% berberine either by itself or combined with sulfacetamide demonstrated significant symptom improvement and tested negative for *Chlamydia trachomatis*, with no relapse after 1 year.

A later comparison-controlled clinical study also evaluated the effectiveness of the topical treatment of berberine for trachoma in 32 microbiologically confirmed patients (Khosla et al 1992). A 0.2% berberine solution (2 drops in each eye, three times daily) was found to be more effective than sulfacetamide (20%) in reducing both the course of the trachoma and the serum antibody titres against *C. trachomatis*. Berberine eyedrops were compared to berberine plus neomycin ointment, sulfacetamide and placebo in a double-blind, controlled clinical trial in 96 primary school children (Mohan et al 1982). Patients in the berberine group were asked to use 2 drops (0.2% berberine) of the solution in each eye, three times daily and to additionally apply a berberine ointment (0.2%) at night for 3 months. Children treated with only the berberine had an 87% clinical response rate, compared to 58% in the berberine and neomycin group; however, only 50% tested negative in follow-up microbiological tests.

A study addressed safety concerns about berberine eye products (Chignell et al 2007). They concluded that caution should be taken when eyes are exposed to strong sunlight.

Hypercholesterolaemia

In an RCT, oral doses of 0.5 g of berberine, given twice daily for 3 months in 32 hypercholesterolaemic patients, resulted in a 29% reduction in serum cholesterol, a 35% reduction in triglycerides and a 25% reduction in LDL cholesterol (Kong et al 2004). HDL cholesterol levels remained unchanged. Berberine also significantly improved liver function, as noted by liver enzyme levels. A later trial compared berberine, simvastatin and a combination of both (Kong et al 2008). Patients (n = 63) diagnosed with hypercholesterolaemia (total cholesterol over 5.2 mmol/L) were randomised into three groups and given either berberine (1 g/day), simvastatin (20 mg/day) or both. After 2 months of oral treatment, the results were as follows: monopreperation of berberine reduced LDL cholesterol by 23.8% and triglycerides by 22.1%; simvastatin reduced LDL cholesterol by 14.3% and triglycerides by 11.4%; combination therapy reduced LDL cholesterol by 31.8% and triglycerides by 38.9%. Total cholesterol reductions were similar to LDL reductions and HDL cholesterol did not change significantly in any group. All preparations were found to be safe.

Chronic congestive heart failure

The efficacy and safety of berberine in chronic congestive heart failure were studied in a randomised, double-blind, controlled study in 156 patients with chronic heart failure (Zeng et al 2003). All patients received conventional treatment and 79 patients in the treatment group also received 1.2–2.0 g/day of berberine for 8 weeks. Quality of life was greatly improved in the berberine group in comparison to controls, as measured by a significant increase in left ventricular ejection fraction, less fatigue and a greater capacity to exercise. A significant reduction in mortality was also noted during the 24-month follow-up (7 in the treatment group as compared to 13).

The acute cardiovascular effects of intravenous berberine (0.02 and 0.2 mg/kg/min for 30 min) were studied in 12 patients with refractory congestive heart failure (Marin-Neto et al 1988). At the lower dose, a 14% reduction in heart rate was noted, whereas 0.2 mg/kg resulted in a 48% decrease in systemic vascular resistance and a 41% decrease in pulmonary vascular resistance. Right atrium and left ventricular end-diastolic pressures were reduced by 28% and 32%, respectively. Cardiac index, stroke index and left ventricular ejection fraction were also significantly enhanced.

Diabetes

A pilot study was designed to determine the safety and efficacy of berberine in patients with type 2 diabetes mellitus (Yin et al 2008). Eighty-four subjects were divided into two groups. Study A consisted of 36 newly diagnosed type 2 diabetics who received either berberine (500 mg 3 times daily) or metformin (500 mg 3 times daily) for 13 weeks. The second group (study B) consisted of 48 diabetics who were poorly controlled on their current medication. They all stayed on their current regimen

and half also received berberine (500 mg 3 times daily) for 13 weeks.

Results for study A: Participants in the berberine group had very similar results to the metformin group. Haemoglobin A_{1c} reduced by 2%, fasting blood glucose reduced by 3.8 mmol/L and postprandial blood glucose reduced by 8.8 mmol/L. Fasting insulin levels and postprandial insulin were also the same as the metformin group. Total cholesterol (reduced by 0.57 mmol/L) and triglycerides (reduced by 0.24 mmol/L) were significantly lower after 13 weeks as compared to the metformin group ($P = 0.05$).

Results for study B: Participants in the combination group had reductions in haemoglobin A_{1c} from 8.1% to 7.3% ($P = 0.001$). Fasting blood glucose and postprandial blood glucose also improved significantly ($P = 0.001$). Fasting insulin was reduced by 29.0% and LDL cholesterol, total cholesterol and triglycerides were also significantly lower than baseline after 13 weeks.

Radiation-induced lung injury (RILI)

A prospective, randomised, placebo-controlled, double-blind trial was designed to determine whether berberine might reduce RILI in patients receiving radiation treatment for non-small cell lung cancer (Liu et al 2008). Ninety patients were randomised to receive either 20 mg/kg/day of berberine or placebo for 6 weeks during three-dimensional conformal radiation therapy. At 6 weeks, 45.2% of patients in the treatment group developed RILI as compared to 72.1% in the placebo group. At 6 months, 35.7% of patients in the berberine group experienced RILI as compared to 65.1% in the control group. Significant improvements in lung function were also demonstrated.

OTHER USES

Menorrhagia, dysmenorrhoea, peptic ulcer, gastritis, dyspepsia, skin disorders, sinusitis, chronic inflammation of mucous membranes and topically for ulceration and infection.

Traditionally, it is used as a bitter digestive stimulant that improves bile flow and liver function.

DOSAGE RANGE

Internal

- Tincture (1:3): 2.0–4.5 mL/day or 15–30 mL/week (Bone 2003).
- Tincture (1:10): 6–12 mL/day (Mills & Bone 2005).
- Dried rhizome and root: 1.5–3 g/day by decoction (Mills & Bone 2005).

External

- Eyewash: 0.2% berberine solution, 2 drops in each eye, three times daily (Khosla et al 1992).

ADVERSE REACTIONS

Goldenseal is generally regarded as safe in recommended doses (Blumenthal 2003). Doses higher than 0.5 g of pure berberine may cause lethargy, dizziness, dyspnoea, skin and eye irritation, gastrointestinal irritation, nausea, vomiting, diarrhoea, nephritis and kidney irritation (Blumenthal et al 1998).

Clinical note — Berberine absorption

Berberine is poorly absorbed, with up to 5% bioavailability (Pan et al 2002). In vitro data have clearly demonstrated that berberine is a potent antibacterial; however, in vivo data have established low bioavailability. Berberine has been shown to upregulate the expression and function of the drug transporter P-glycoprotein (Pgp) (Lin et al 1999). Pgp belongs to the super family of ATP-binding cassette transporters that are responsible for the removal of unwanted toxins and metabolites from the cell (Glastonbury 2003). It appears that Pgp in normal intestinal epithelia greatly reduces the absorption of berberine in the gut. In vivo and in vitro methods have been used to determine the role of Pgp in berberine absorption by using the known Pgp inhibitor cyclosporin A (Pan et al 2002). Co-administration increased berberine absorption sixfold and clearly demonstrated the role of Pgp in absorption.

Increased expression of Pgp can lead to cells displaying multidrug resistance (Glastonbury 2003). As previously reported, a certain flavonolignan in many *Berberis* spp. has the ability to inhibit the expression of multidrug-resistant efflux pumps (Stermitz et al 2000a, 2000b), allowing berberine and certain antibiotics to be more effective.

SIGNIFICANT INTERACTIONS

Because controlled studies are not available, interactions are currently speculative and based on evidence of pharmacological activity. Many studies have shown that extracts of goldenseal significantly inhibit cytochrome P450 enzymes (Budzinski et al 2000, 2007, Etheridge et al 2007, Gurley et al 2005, 2008a, 2008b, Raner et al 2007). The inhibitory effects of berberine on CYP3A4/5, CYP2C8, CYP2D6 and CYP2E1 have been reported in vitro with one study finding that CYP2D6 and CYP3A4/5 were each down-regulated by 40% (Gurley et al 2005). Two studies in healthy volunteers demonstrated that CYP3A4 and CYP2D6 were significantly down-regulated (Gurley et al 2008a, 2008b). Theoretically, these findings suggest that any drug metabolised using this pathway may be affected. The clinical relevance of this possible interaction is unknown.

Cyclosporin A

Berberine increased the blood concentration of cyclosporin A in renal transplant patients in an RCT (Wu et al 2005): 52 patients received 0.2 g of berberine orally three times daily for 3 months. The final blood concentration in the berberine/cyclosporin A group was 29.3% higher than the group given cyclosporin A only. The relevance of this to oral ingestion of goldenseal is unknown — caution advised.

Digoxin

Twenty healthy volunteers took 3210 mg of goldenseal and 0.5 mg digoxin daily for 14 days (Gurley

et al 2007). There was no change in the pharmacokinetics of digoxin suggesting that this dose of goldenseal is not a potent modulator of Pgp.

CONTRAINDICATIONS AND PRECAUTIONS

Goldenseal is contraindicated in kidney disease because of inadequate excretion of the alkaloids (Blumenthal 2003). Berberine has been found to be a potent displacer of bilirubin (Chan 1993). A review published in 1996 stated that berberine can cause severe acute haemolysis and jaundice in babies with glucose-6-phosphate dehydrogenase deficiency (Ho 1996). Goldenseal is therefore not recommended in pregnancy, lactation or cases of neonatal jaundice. Goldenseal is also contraindicated in hypertension (BHMA 1983) as large amounts of hydrastine have been reported to restrict peripheral blood vessels and cause hypertension (Genest & Hughs 1969). The dose required to induce this effect is unknown and the ability to reach this threshold using the whole extract is unlikely; however, until this is clarified goldenseal is best avoided in hypertension.

PREGNANCY USE

Contraindicated in pregnancy and lactation.

In addition to the preceding concerns about bilirubin, berberine has caused uterine contractions in pregnant and non-pregnant experimental models (Mills & Bone 2005). An in vivo study using 65-fold the average human oral dose of goldenseal investigated effects on gestation and birth and found no increase in implantation loss or malformation (Yao et al 2005). The authors conclude that the low bioavailability of goldenseal from the gastrointestinal tract was likely to explain the differences between in vitro and in vivo effects in pregnancy. Hydrastine (0.5 g) has also been found to induce labour in pregnant women (Mills & Bone 2005). Until more pharmacokinetic studies are done, goldenseal is best avoided in pregnancy.

PRACTICE POINTS/PATIENT COUNSELLING

- Goldenseal has been used traditionally as an antidiarrhoeal agent and digestive stimulant.
- It has been used topically as a wash for sore or infected eyes and as a mouth rinse.
- Goldenseal is a bitter digestive stimulant that improves bile flow and liver function.
- Most clinical evidence has been conducted using the chemical constituent berberine. These data have shown effectiveness against diarrhoea, congestive heart failure, infection and cholesterol.
- Goldenseal is not to be used in pregnancy or during breastfeeding.
- Use with caution in patients who have hypertension or taking cyclosporin.

PATIENTS' FAQs

What will this herb do for me?

Goldenseal may be used in the treatment of diarrhoea, dyspepsia, infection, diabetes and cholesterol. Most of the available research has been done on the alkaloid berberine. More clinical trials of the whole extract are needed to determine if the same effect will be seen.

When will it start to work?

Antibacterial and antidiarrhoeal activities should be apparent quite quickly. The lipid-lowering effects of goldenseal have been reported within 12 weeks.

Are there any safety issues?

The herb should not be taken during pregnancy or lactation and may interact with some medications.

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Grapeseed extract

HISTORICAL NOTE Since the time of Ancient Greece, grape leaves, fruit and sap have been used medicinally to treat a variety of ailments, such as skin and eye irritation, varicose veins, diarrhoea, bleeding and cancer. In the 1500s, a French expedition in North America found itself trapped in ice and forced to survive on salted meat and stale biscuits. After a time, the crew began to show signs of what we now recognise as scurvy. It is believed that the men survived because a Native American Indian showed them how to make a tea from the bark and needles of pine trees. The French explorer wrote of this encounter in a book that was subsequently read by researcher Jacques Masquelier, also a Frenchman, in the 20th century. Intrigued by the story, he began to investigate the chemistry and properties of pine bark and identified oligomeric proanthocyanidin complexes (OPCs). Several years later, he extracted OPCs from grapeseed extract (GSE), which is now considered the superior source of OPCs (Murray & Pizzorno 1999).

COMMON NAME
Grapeseed extract

BOTANICAL NAME/FAMILY
Vitis vinifera/Vitaceae

PLANT PARTS USED
Seeds, grape skins

CHEMICAL COMPONENTS
The skin of the grapeseed is a rich source of proanthocyanidins (also referred to as procyanidins). Mixtures of procyanidins are referred to as OPCs. Grapeseed extract contains OPCs made up of dimers or trimers of (+)-catechin and (–)-epicatechin (Fine 2000) and also trimers and polymers of proanthocyanidins. *Vitis vinifera* also contains stilbenes (resveratrol and viniferins) (Bavaresco et al 1999); however, it is unclear whether significant amounts are present in the seeds.

MAIN ACTIONS
Most evidence of activity derives from in vitro and animal studies for OPCs or GSE; however, some clinical studies are also available. The stilbene resveratrol (3,4′,5 trihydroxystilbene) has also been the focus of much investigation and exhibits anti-inflammatory, antithrombotic, anticarcinogenic and antibacterial activities, but it is uncertain whether significant amounts are present in the seeds and GSE (Fremont 2000).

Antioxidant

Grapeseed PC extract has demonstrated excellent free radical scavenging abilities, in both test tube and animal models, and provided significantly greater effects than vitamins C, E and beta-carotene (Bagchi et al 1997, 1998, 2000, 2001, Castillo et al 2000, Facino et al 1999, Fauconneau et al 1997, Maffei et al 1994, 1996). In vitro tests have further identified a vitamin E sparing effect, in which PCs prevent vitamin E loss and cause alpha-tocopherol radicals to revert to their antioxidant form (Maffei et al 1998).

Inhibits platelet aggregation

Grapeseed extract has been shown to inhibit platelet aggregation, and combining extracts of grapeseed and grape skin produces a far greater antiplatelet effect in test tube and ex vivo tests (Shanmuganayagam et al 2002). Inhibition of platelet function was confirmed more recently (Sano et al 2005, Vitseva et al 2005).

Stabilises capillary walls and enhances dermal wound healing

In vivo studies have found that PCs stabilise the capillary wall and prevent increases in capillary permeability when chemically induced in tests, such as carrageenan-induced hindpaw oedema (Zafirov et al 1990) and dextran-induced oedema (Robert et al 1990). Components in GSE have the ability to cross-link collagen fibres, thereby strengthening the collagen matrix (Tixier et al 1984). Clinical studies confirm that grapeseed extract improves capillary resistance when used at a dose of 150 mg daily (Lagrue et al 1981). Not unexpectedly, research has also identified wound-healing properties.

A 2002 study in mice found that topical application of grapeseed PCs considerably accelerated wound contraction and closure and provided additional support during the wound healing process (Khanna et al 2002). It has been shown that a GSE preparation containing 5000 ppm resveratrol facilitates oxidant-induced vascular endothelial growth factor expression in keratinocytes in vitro, which may account for its beneficial effects in promoting dermal wound healing and resolution of related skin disorders (Khanna et al 2001).

Anticarcinogenic, antimutagenic

Most tests have been conducted with PCs from grapeseed extract and show significant activity.

Several in vitro studies have demonstrated that PCs from *Vitis vinifera* strongly suppress tumour growth and have cytotoxic activity against a range of cancer cells, including breast, lung, prostate, colon and gastric adenoma cells (Bagchi et al 2000, Engelbrecht et al 2007, Joshi et al 2001, Kaur et al 2006, Tyagi et al 2003, Ye et al 1999). More specifically, PCs from grapeseeds exerted antitumour properties in several animal models (Kim et al 2004, Martinez Conesa et al 2005, Nomoto et al 2004, Ray et al 2005, Raina et al 2007, Zhang et al 2005). One study also found that grapeseed PCs enhanced the growth and viability of human gastric mucosal cells at the same time (Ye et al 1999).

Tests with GSE showed that it induced apoptosis in acute myeloid leukaemic cells (Hu & Qin 2006). A recent in vitro study identified gallic acid within GSE to be effective against human prostate carcinoma cells (Agarwal et al 2006). In breast cancer cells, its mechanism of action is to inhibit aromatase activity and expression (Kijima et al 2006). A phase 1 chemoprevention trial in postmenopausal women is being carried out which hypothesises that breast cancer risk will be reduced with GSE due to the antiaromatase activity (Palomares et al 2006).

Clinical note — Proanthocyanidins

Proanthocyanidins (PCs) are a group of naturally occurring polyphenolic bioflavonoids that are present in many fruits (e.g. apples, pears, grapes and peaches), vegetables, nuts, beans (e.g. cocoa), seeds, flowers and bark (e.g. pine) (Bavaresco et al 1999). Grapeseeds are a particularly rich source of PCs, containing more than any other grape products, such as red, white or rose wine or grape juice, and more than most commonly available foods (Rasmussen et al 2005). Proanthocyanidins are also found in many medicinal herbs, such as *Ginkgo biloba*, *Camellia sinensis*, *Hypericum perforatum* and *Crataegus monogyna*; however, GSE is considered the superior source. Proanthocyanidins demonstrate a wide range of biological actions according to various in vitro, in vivo and clinical studies. However, in recent years, bioavailability studies have demonstrated that not all orally ingested PCs are absorbed. In particular, PC polymers have negligible absorption from the gastrointestinal tract, whereas low-molecular-weight PCs (monomers, dimers and trimers) are absorbed (Rasmussen et al 2005). In addition, some PCs are degraded by microflora in the caecum and large intestine into low-molecular-weight phenolic acids, chiefly hydroxyphenylpropionic acid and 4-O-methylgallic acid (Ward et al 2004), which are likely to contribute to the biological effects. These findings have implications when interpreting in vitro data because this method of testing does not take into account the variations in bioavailability and metabolism in the body.

Anti-inflammatory

In vitro evidence suggests that GSE has anti-inflammatory activity (Sen & Bagchi 2001). Two compounds isolated from *Vitis vinifera* exhibit non-specific inhibitory activity against COX-1 and -2 (Waffo-Teguo et al 2001). Inhibition of the pro-inflammatory 5-lipoxygenase is another mechanism identified recently for GSE (Leifert & Abeywardena 2008). Rats fed on a hyperlipidic diet and GSE had a reduction in proinflammatory markers such as CRP, IL-6 and TNF-alpha (Terra et al in press).

Cardioprotective effects

Considering that GSE demonstrates antioxidant, antiplatelet and anti-inflammatory actions, it may have a role in the prevention of cardiovascular disease. A number of researchers have investigated this issue further, mainly using animal models. One series of studies was conducted by Bagchi et al (2003) using a natural, standardised, water–ethanol

extract made from California red grapeseeds, which contained approximately 75–80% oligomeric PCs and 3–5% monomeric PCs. According to in vivo research, treatment with GSE provided resistance to myocardial ischaemia-reperfusion injury, better postischaemic ventricular recovery and reduced incidence of reperfusion-induced ventricular fibrillation and ventricular tachycardia, as compared with corresponding control animals. Another study using a hamster atherosclerosis model found that 50 and 100 mg GSE/kg body weight led to a 49% and 63% reduction in foam cells, respectively. Additionally, cholesterol and triglyceride lowering activity has been reported (Yu et al 2002). One animal study identified that GSE significantly reduced total cholesterol by 42%, LDLs by 56% and elevated HDL cholesterol by 56% (El-Adawi et al 2006).

A more recent study with hyperlipidaemic rabbits showed that GSE administered over 15 weeks produced a significant reduction in aortic atherosclerosis in males, although no effect was observed in females (Frederiksen et al 2007).

Cognition enhancer/neuroprotective

Grapeseed proanthocyanidin (GSPE) demonstrated neuroprotective effects in vivo and an increase in superoxide dismutase with the highest test dose (Devi et al 2006). Some in vivo studies have identified that GSE reduces age-related oxidative DNA damage and improves memory performance and cognitive enhancement, most likely achieved via an antioxidant mechanism (Balu et al 2005, 2006, Sarkaki et al 2007, Sreemantula et al 2005). Interestingly, along with GSE's antioxidant action, one study demonstrated a neurorescue effect when GSE was given to rats 3 hours after neurotoxic injury (Feng et al 2005, 2007).

The ability of GSE to protect critical proteins in the brain that are most affected in Alzheimer's disease suggests a potential clinical application (Kim et al 2005, 2006).

Reducing drug-induced toxicity

Protection against chemically induced multiorgan toxicity has also been reported (Bagchi et al 2001). Hepatoprotection was demonstrated in studies where rats were exposed to a hepatotoxin. It is thought that this effect was due to inhibiting lipid peroxidation via antioxidant activity (Dulundu et al 2007, Jamshidzadeh et al 2008). GSE demonstrated potent antioxidant activity and protected kidneys from gentamicin-induced nephrotoxicity in an experimental model. The same study found that bone marrow chromosomes were also protected (El-Ashmawy et al 2006). GSE was also protective in rats from toxicity due to radiation exposure (Enginar et al 2007, Saada et al 2009).

GSE protected against the cardiotoxic side effects of the chemotherapy drug doxorubicin in vivo. It is thought that the antioxidant properties of GSE protecting cardiomyocytes was chiefly responsible (Du & Lou 2008). Protection against chemotherapy-induced small intestine mucositis was observed in another animal study where rats were administered with 400 mg/kg of GSE before and during chemotherapy (Cheah et al 2008).

OTHER ACTIONS

There is preliminary evidence from many other studies indicating a range of pharmacological effects. Results from a clinical study suggest that GSE increases the rhodopsin content of the retina or accelerates its regeneration after exposure to bright light (Boissin et al 1988). Reduced incidence of cataract development and cataract progression was also observed in an experimental model using grapeseed proanthocyanidin extract (GSPE) (Durukan et al 2006). GSE shows evidence of antibacterial and antifungal actions specifically against *Candida albicans* (Han 2007, Furiga et al 2008). GSE has also been shown in vitro to have an anti-venom action against the saw-scaled viper (Mahadeswaraswamy et al 2008). Antinociceptive effects demonstrated in vivo for GSE show a reduction in pain and a potentiating effect of morphine (Uchida et al 2008). An animal study demonstrated anti-ageing potential due to GSE maintaining the erythrocyte membrane integrity that is often impaired in the elderly (Sangeetha et al 2005).

CLINICAL USE

Free radical damage has been strongly associated with virtually every chronic degenerative disease, including cardiovascular disease, arthritis and cancer. Clearly, due to the potent antioxidant activity of grapeseed, its therapeutic potential is quite broad. Most clinical studies have been conducted in Europe using a commercial product known as Endotelon®. Due to the poor bioavailability of high-molecular-weight PCs, it is advised that products containing chiefly low-molecular-weight PCs be used in practice.

Fluid retention, peripheral venous insufficiency and capillary resistance

There is good supportive evidence from clinical studies that have investigated the use of GSE in fluid retention, capillary resistance or venous insufficiency (Amsellem et al 1987, Delacroix 1981, Constantini et al 1999, Henriet 1993, Lagrue et al 1981).

Hormone replacement therapy and fluctuations in hormone levels can produce symptoms of venous insufficiency in some women. One large study involving 4729 subjects with peripheral venous insufficiency due to hormone replacement therapy (HRT) showed that GSE decreased the sensation of heaviness in the legs in just over half the subjects by day 45, whereas 89.4% of subjects experienced an improvement by day 90 (Henriet 1993). According to an open multicentre study of women aged 18–50 years with oedema due to premenstrual syndrome, GSE (Endotelon®) administered from day 14 to 28 improved various symptoms of fluid retention such as abdominal swelling, weight gain and pelvic pain and also venous insufficiency (Amsellem et al 1987). The treatment was taken for four cycles, with most women (60.8%) responding after two cycles and 78.8% responding after four cycles.

An open study involving 24 patients with non-complicated chronic venous insufficiency found that over 80% of subjects receiving OPCs (100 mg/day) reported lessened or no symptoms after

10 days. Symptoms of itching and pain responded best, completely disappearing during the course of treatment in 80% and 53% of the patients, respectively (Costantini et al 1999). A double-blind study of 50 patients with symptoms of venous insufficiency found that GSE (Endotelon® 150 mg daily) improved both subjective and objective markers of peripheral venous insufficiency, such as pain (Delacroix 1981).

In some pathological conditions, such as inflammation or diabetes, vascular permeability can be abnormally increased (Robert et al 1990). Two studies investigated the effects of GSE on capillary resistance in hypertensive and diabetic patients under both open and double-blind, placebo-controlled conditions with treatment producing significant improvements in both groups (Lagrue et al 1981). The studies used a daily dose of 150 mg (Endotelon®).

Diabetes

Diabetic retinopathy

Grapeseed extract (Endotelon® 150 mg) was found to stabilise diabetic retinopathy in 80% of subjects compared to 47% with placebo, under double-blind test conditions (Arne 1982). These results were obtained by measuring objective markers such as visual acuity, muscular tone and ocular tone.

Diabetic nephropathy

Preliminary in vitro research indicates that grapeseed polyphenols have a protective effect against cell damage, including renal cell damage, caused by high glucose levels (Fujii et al 2006). Other in vitro research also points to possible therapeutic benefits in preventing and treating vascular problems and diabetic complications (Zhang et al 2007).

A study with diabetic rats given grapeseed proanthocyanidins extracts (GSPE) identified nephroprotection, which might be related to the free radical scavenging activity of GSPE (Liu et al 2006). Further research would be required to confirm a clinical application.

Eye strain

A double-blind study involving 75 patients with eye strain caused by viewing a computer screen found that a dose of GSE 300 mg daily significantly improved objective and subjective measures (Bombardelli & Morrazzoni 1995). Grapeseed extract (Endotelon®) has also been shown to significantly improve visual adaptation to and from bright light in a dual centre study involving 100 volunteers (Boissin et al 1988, Corbe et al 1988). A dose of 200 mg daily over 5 weeks was used. It has been proposed that GSE increases rhodopsin content of the retina or accelerates its regeneration after exposure to bright light.

Hyperlipidaemia/atherosclerosis

A recent single-blind, placebo study where 61 healthy subjects took 200 or 400 mg GSE over 12 weeks showed that active treatment significantly lowers oxidised LDL levels at the end of the test period. The group receiving the higher dose experienced results at the earlier 6-week point as well as at 12 weeks (Sano et al 2007). A randomised, double-blind study of 40 subjects with hypercholesterolaemia compared the effects of placebo, chromium polynicotinate (400 microgram/day), GSE (200 mg/day) or a combination of both. Over 2 months, the combination treatment decreased total cholesterol and LDL levels significantly but did not significantly alter homocysteine, HDL or blood pressure among the four groups (Preuss et al 2000). The role of GSE in achieving this result is unclear.

Enhances dermal wound healing

A 2002 study in mice found that topical application of grapeseed PCs considerably accelerate wound contraction and closure and provided additional support during the wound healing process (Khanna et al 2002).

Chloasma

Chloasma is a condition characterised by hyperpigmentation and is generally considered recalcitrant to treatment. Proanthocyanidin-rich GSE successfully reduced hyperpigmentation in women with chloasma after 6 months of oral treatment, according to an open study involving 12 subjects (Yamakoshi et al 2004). The study continued for another 6 months but failed to find an additional improvement with further use. The researchers suggested that a preventative effect may be possible with long-term oral GSE when used in the months prior to summer.

Pancreatitis

It is believed that the oxygen-derived free radicals mediate tissue damage in acute and chronic pancreatitis. Therefore, antioxidant treatment is being investigated. A small, open study of three patients with difficult-to-treat chronic pancreatitis found that a commercially available IH636 GSE produced a reduction in the frequency and intensity of abdominal pain, as well as resolution of vomiting in one patient.

Preventing reperfusion injury

Procyanidin administration reduced the adverse effects of myocardial ischaemia-reperfusion injury during cardiac surgery in several in vivo studies (Facino et al 1999, Maffei et al 1996). This appears to be positively associated with an increase in plasma antioxidant activity. An animal model also suggests that a proanthocyanidin-rich extract from GS was protective against renal damage from ischaemia-reperfusion injury (Nakagawa et al 2005). Another animal model showed protection against hepatic ischaemia/reperfusion injury by regulating the release of inflammatory mediators and by its antioxidant action (Sehirli et al 2008).

Reduces sun burn

Topical application of GSE has been shown to enhance sun protection factor in human volunteers (Bagchi et al 2000). A recent study, with a GSE supplement, topical cream and a topical lotion (both Anthogenol products), assessed 42 individuals randomised into two groups with one group taking

the dietary supplement. UV radiation-induced erythema was treated and it was found that both the topical applications decreased erythema formation with slightly better results for those volunteers also taking the oral supplements. Application of the topical lotion produced the best results (53% reduction) and the lotion plus the GSE supplement added a further 13% reduction in skin inflammation while all groups found improved skin hydration (Hughes-Formella et al 2007).

Protection against multi-organ drug and chemical toxicity

The results from a number of in vivo studies have suggested that pre-exposure to grapeseed extract can provide multiorgan protection against damage caused by various drugs, such as paracetamol, amiodarone, doxorubicin, cadmium chloride and dimethylnitrosamine treatment (Bagchi et al 2000, 2001).

OTHER USES

Some preliminary in vitro research suggests a potential use for periodontal diseases and oral hygiene for prevention of periodontitis. This is due to GSE's antimicrobial effect against specific oral bacteria and its strong antioxidant action (Houde et al 2006, Furiga et al in press).

An in vitro study suggests a promising use for GSE as active against *Candida albicans* and a possible synergistic action with the drug amphotericin B, which would enable this strong drug dose to be reduced by 75% when given in conjunction with GSE. Clinical studies are needed to confirm this potential use (Han 2007).

DOSAGE RANGE

- Fluid extract 1:1 (g/mL): 20–40 mL per week.
- Solid dose forms: 12,000 mg of GSE standardised to OPCs taken 2–3 times daily in order to provide 150–300 mg of OPCs daily. Due to the poor bioavailability of high-molecular-weight PCs, it is advised that products containing chiefly low-molecular-weight PCs be used in practice.

According to clinical studies:

- Chloasma: 162 mg/day GSE.
- CVD: 200–300 mg/day GSE.
- Hypercholesterolaemia: 200–400 mg/day GSE.
- Chronic pancreatitis: ActiVin® 200–300 mg/day.
- Oedema due to premenstrual syndrome: GSE (Endotelon®) 150–400 mg taken from day 14 to 28.
- Oedema due to injury or surgery: 200–400 mg/day GSE (Endotelon ®).
- Diabetic retinopathy: 150–400 mg/day GSE (Endotelon®).
- Vascular fragility: 150–400 mg/day GSE (Endotelon®).
- Venous insufficiency and poor leg circulation: GSE (Endotelon®) 150–300 mg/day.
- Vision problems: GSE (Endotelon®) 200 mg/day.

TOXICITY

Tests in animal models have found GSE to be extremely safe (Bentivegna & Whitney 2002).

ADVERSE REACTIONS

Studies using doses of 150 mg/day have found it to be well tolerated. Side effects are generally limited to gastrointestinal disturbances, including nausea and indigestion.

SIGNIFICANT INTERACTIONS

Controlled studies are not available; therefore, interactions are theoretical and based on evidence of pharmacological activity.

Antiplatelet drugs

Additive effect theoretically possible — observe patient.

Anticoagulant drugs

Increased risk of bleeding theoretically possible — monitor patient for increased bruising or bleeding.

Iron and iron-containing preparations

Decreased iron absorption. Tannins can bind to iron, forming insoluble complexes — separate doses by 2 hours.

CONTRAINDICATIONS AND PRECAUTIONS

None known.

PREGNANCY USE

Safety has not been scientifically established.

PRACTICE POINTS/PATIENT COUNSELLING

- Grapeseed extract has considerable antioxidant activity and appears to regenerate alpha-tocopherol radicals to their antioxidant form.
- Grapeseed extract also has anti-inflammatory actions, reduces capillary permeability, enhances dermal wound healing and reduces photodamage, inhibits platelet aggregation and may enhance rhodopsin regeneration or content in the retina.
- It is popular in Europe as a treatment for venous insufficiency and capillary fragility, both of which are supported by clinical evidence. It is also used to relieve eye strain, stabilise diabetic retinopathy and connective tissue disorders.
- Preliminary research has identified cardioprotective effects due to a variety of mechanisms. Possible benefits in pancreatitis and multiorgan protection against damage caused by several pharmaceutical drugs, including several chemotherapy drugs, and radiation. Anticarcinogenic activity has also been reported.
- It shows promise for neurodegenerative disorders in preliminary studies.
- Most clinical research has been conducted in Europe with a commercial grapeseed product known as Endotelon®.
- Due to concerns with bioavailability, it is recommended that only preparations containing low-molecular-weight PCs be used.

PATIENTS' FAQs

What will this herb do for me?

There is evidence that GSE is a useful treatment for venous insufficiency, poor leg circulation and

capillary fragility and has considerable antioxidant activity. It is also used to treat eye strain, diabetic retinopathy and enhance wound healing when applied locally.

When will it start to work?

It appears to relieve symptoms of venous insufficiency within 10 days and eye strain within 5 weeks. Other uses may take longer before results are seen.

Are there any safety issues?

Research suggests that it is well tolerated and generally safe; however, people taking anticoagulant medicines should refer to their healthcare professional before taking this substance.

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Green tea

HISTORICAL NOTE Tea has been a popular beverage for thousands of years and was originally grown in China, dating back 5000 years, where it has been used as part of various ceremonies and to maintain alertness. Green tea and the partially fermented oolong tea have remained popular beverages in Asia since that time, whereas black tea is the preferred beverage in many English-speaking countries. Tea was introduced to the Western culture in the 6th century by Turkish traders (Ulbricht & Basch 2005). Second to water, tea is now considered to be the world's most popular beverage.

COMMON NAME
Green tea

OTHER NAMES
Chinese tea, camellia tea, gruner tea, Matsu-cha, Green Sencha Tea, Japanese tea, Yame tea

BOTANICAL NAME/FAMILY
Camellia sinensis (family Theaceae)

PLANT PART USED
Leaf

CHEMICAL COMPONENTS
The composition of green tea varies according to the growing and harvesting methods, but the most abundant components are polyphenols, which are predominantly flavonoids (e.g. catechin, epicatechin, epicatechin gallate, epigallocatechin gallate, proanthocyanidins). Caffeine content in green tea varies but is estimated at about 3%, along with very small amounts of the other common methylxanthines, theobromine and theophylline (Graham 1992). It also contains many other constituents, such as tannin, diphenylamine, oxalic acid, trace elements and vitamins.

Epigallocatechin gallate is one of the most abundant polyphenols in tea and is regarded as the most important pharmacologically active component.

MAIN ACTIONS
It is suspected that the polyphenol content is chiefly responsible for the chemoprotective, antiproliferative, antimicrobial and antioxidant activity of green tea. The caffeine content is predominantly responsible for central nervous system activity and an interaction between both appears necessary for increasing thermogenesis.

Antioxidant
Green tea has consistently demonstrated strong antioxidant activity. In a controlled human trial, 24 healthy women consumed two cups of green tea (250 mg catechins/day) for 42 days (Erba et al 2005). The results showed a significant increase in plasma antioxidant status, reduced plasma peroxides and reduced LDL cholesterol when compared with controls. Several other in vitro animal and human studies have also demonstrated that green tea inhibits lipid peroxidation and scavenges hydroxyl and superoxide radicals (Leenen et al 2000, Rietveld & Wiseman 2003, Sung et al 2000).

Clinical note — The difference between teas
Black, green and oolong tea are produced from the same plant (*Camellia sinensis*) but differ in polyphenol content according to the way the leaves are processed. Black tea is made from oxidised leaves, whereas oolong tea is made from partially oxidised leaves and green tea leaves are not oxidised at all. Because the oxidising process converts many polyphenolic compounds into others with less activity, green tea is considered to have the strongest therapeutic effects and the highest polyphenol content (Lin et al 2003). Caffeine concentrations also vary between the different teas: black tea > oolong tea > green tea > fresh tea leaf (Lin et al 2003). Variation in caffeine content is further influenced by growing conditions, manufacturing processes and size of the tea leaves (Astill et al 2001). The highest quality leaves are the first spring leaf buds, called the 'first flush'. The next set of leaf buds produced is called the 'second flush' and considered to be of poorer quality. Tea varieties also reflect the area they are grown in (e.g. Darjeeling in India), the form produced (e.g. pekoe is cut, gunpowder is rolled) and processing method (black, oolong or green) (Ulbricht & Basch 2005).

Antibacterial activity
Green tea extract has moderate and wide-spectrum inhibitory effects on the growth of many types of pathogenic bacteria, according to in vitro tests, including seven strains of *Staphylococcus* spp, seven strains of *Streptococcus* spp, one strain of *Corynebacterium suis*, 19 strains of *Escherichia coli* and 26 strains of *Salmonella* spp (Ishihara et al 2001). Green tea was effective against most of the 111 bacteria tested including two genera of gram-positive and seven genera of gram-negative bacteria. It was also confirmed that in vivo it could protect against *Salmonella typhimurium* (Bandyopadhyay et al 2005). Green tea has also been found to inhibit *Helicobacter pylori* in an animal model (Matsubara et al 2003). According to one study, which compared the antibacterial activity of black, green and oolong tea, it seems that fermentation adversely affects antibacterial activity, as green tea exhibited the strongest effects, and black tea the weakest (Chou et al 1999). An in vitro study has demonstrated that green tea can significantly lower bacterial endotoxin-induced cytokine release and therefore may reduce mortality from sepsis.

Oral pathogens

Both in vitro and in vivo tests have identified strong antibacterial activity against a range of oral pathogens, such as *Streptococcus mutans*, *S. salivarius* and *E. coli* (Otake et al 1991, Rasheed & Haider 1998). The mechanism of action appears to involve anti-adhesion effects, with the strongest activity associated with epigallocatechin gallate and epicatechin gallate. Green tea catechins (GTCs) have also showed an antibacterial effect against *Porphyromonas gingivalis* and *Prevotella* spp in vitro (Hirasawa et al 2002). Furthermore, green tea polyphenols, especially epigallocatechin gallate, have been found to completely inhibit the growth and adherence of *P. gingivalis* on buccal epithelial cells (Sakanaka et al 1996).

Antiviral activity

A number of in vitro studies have shown that epigallocatechin gallate strongly inhibits HIV replication (Chang et al 1994, Fassina et al 2002, Liu et al 2005, Tao 1992, Williamson et al 2006). The theaflavins from black tea have shown even stronger anti-HIV activity in vitro by inhibiting viral entry into target cells (Liu et al 2005). Antiviral activity has also been identified against Epstein–Barr virus, Herpes simplex virus 1 (HSV-1), influenza A and B, rotavirus and enterovirus (Chang et al 2003, Imanishi et al 2002, Isaacs et al 2008, Mukoyama et al 1991, Tao 1992, Weber et al 2003). EGCG and epicatechin gallate (ECG) show antiviral activity inhibiting influenza virus replication in vitro with differences in the strength of the antiviral activity depending on the strain of influenza (Song et al 2005). Antiviral activity seems to be attributable to interference with virus adsorption (Mukoyama et al 1991).

Antimalarial

Antimalarial properties have been shown in vitro with crude extract of green tea, EGCG and ECG strongly inhibiting *Plasmodium falciparum* growth (Sannella et al 2007).

Anticarcinogenic

Several in vitro studies have shown a dose-dependent decreased proliferation and/or increased apoptosis in a variety of cancer cell lines (lung, prostate, colon, stomach, pancreatic, bladder, oral, leukaemia, breast, cervical and bone) (Berger et al 2001, Garcia et al 2006, Gupta et al 2003, Hafeez et al 2006, Kavanagh et al 2001, Kinjo et al 2002, Pianetti et al 2002, Qanungo et al 2005, Qin et al 2007, Sadava et al 2007, Shimizu et al 2005, Srinivasan et al 2008, Valcic et al 1996, Wang & Bachrach 2002, Yoo et al 2002, Zhang et al 2002). Additionally, photochemopreventative effects for green tea and epigallocatechin gallate have been demonstrated in vitro, in vivo and on human skin (Afaq et al 2003) and apoptosis of skin tumour cells (Mantena et al 2005).

The mechanism of action by which tea polyphenols exert antimutagenic and antitumourigenic effects is still largely speculative. However, the following has been observed: inhibition of the large multicatalytic protease and metalloproteinases, which are involved in tumour survival and metastasis, respectively, and inhibition of many tumour-associated protein kinases, while not affecting kinase activity in normal cells (Kazi et al 2002, Wang & Bachrach 2002). Tea polyphenols have also been found to inhibit some cancer-related proteins that regulate DNA replication and transformation. There is increasing evidence that catechins possess anti-angiogenic properties (Sachinidis & Hescheler 2002). Inhibition of angiogenic factors and antitumour immune reactivity including an increase in cytotoxic T lymphocyte cells was found to be the mechanism of action in preventing photocarcinogensis (Mantena et al 2005). Recent work suggests tea polyphenols may inhibit microsomal aromatase and 5 alpha-reductase, so suppressing prostate carcinogenesis. Tea catechins may work to suppress proteasomal activities thereby inhibiting breast cancer cell proliferation (Ho et al 2009).

Antihypertensive

In vitro experiments using green tea extracts have identified angiotensin-converting enzyme inhibition (Persson et al 2006). Animal experiments have also shown that a green tea extract protected against arterial hypertension induced by Angiotensin II (Antonello et al 2007) and green tea lowered blood pressure that had been elevated by a high-cholesterol diet (Song et al 2008). Blood pressure lowering effects have not been demonstrated in humans according to a meta-analysis of parallel group or crossover studies (Taubert et al 2007).

Neuroprotective/neurorescue

Neuroprotective activity refers to the use of an agent before exposure to a neurotoxin which prevents toxicity. Neurorescue is a different term which refers to the use of an agent after exposure to a neurotoxin, which is able to reverse toxicity effects. New in vitro and animal research indicates that (-)-epigallocatechin-3-gallate (EGCG) found in green tea has the ability to act as both a neuroprotective and a neurorescue agent (Hou et al 2008, Guo et al 2007, Jeong et al 2007). In vitro tests reveal EGCG reduces apoptosis of human neuroblastoma cells (Avramovich-Tirosh et al 2007). Additionally, in vivo studies have found a neuroprotective effect for EGCG on dopamine neurons, which is being further investigated as a potential preventative treatment in Parkinson's disease (Guo et al 2007, Jeong et al 2007).

Two animal studies found that EGCG reduced beta-amyloid deposition — one study reported 60% reduction in the frontal cortex and 52% in the hippocampus over the 3 months of the study (Li et al 2006, Rezai-Zadeh et al 2008). This may have implications in the development and progression of Alzheimer's dementia and is being further investigated in other models.

Several different mechanisms of action appear to be responsible for neuroprotective and neurorescue activity including: antioxidant, iron chelating, anti-inflammatory, cell apoptosis, signal transduction, gene regulation and an effect on amyloid precursor protein (APP) (Ostrowska et al 2007, Mandel et al 2006).

Iron chelation

EGCG has been shown to chelate metals such as iron, zinc and copper (Guo et al 1996, Kumamoto et al 2001). Since the accumulation of iron has been implicated in the aetiology of both Alzheimer's dementia and Parkinson's disease and in vivo research shows EGCG's iron-chelating effect penetrates the brain barrier, it may offer neuroprotective and neurorescue effects in these diseases. EGCG has further been shown to reduce APP and beta-amyloid peptide, most likely due to its iron chelating activity (Reznichenko et al 2006). It is possible that iron chelation effects enabling iron to be removed from the brain may provide a novel therapy to prevent progression in neurodegenerative diseases (Mandel et al 2007).

Thermogenic activity

Although the thermogenic activity of green tea is often attributed to its caffeine content, an in vivo study has shown that stimulation of brown adipose tissue thermogenesis occurs to a greater extent than would be expected from the caffeine content alone (Dulloo et al 2000). The interaction between catechin polyphenols and caffeine on stimulating noradrenaline release and reducing noradrenaline catabolism may be responsible. Clinical investigation has produced similar results, with green tea consumption significantly increasing 24-hour energy expenditure and urinary noradrenaline excretion, whereas an equivalent concentration of caffeine had no effect on these measures (Dulloo et al 2000).

OTHER ACTIONS

Green tea exhibits a variety of other pharmacological actions, such as anti-inflammatory activity, central nervous system (CNS) stimulation, inhibition of platelet aggregation, stimulation of gastric acid secretion and diuresis, increased mental alertness, relaxation of extracerebral vascular and bronchial smooth muscle, and reduced cholesterol, triglyceride and leptin levels (Fassina et al 2002, Sayama et al 2000). It has multiple mechanisms that have an impact on the cardiovascular system including lipid lowering, hypocholesterolaemic, anti-inflammatory, antithrombogenic, antioxidant, antihypertensive and anti-atherosclerotic (Babu & Liu 2008). Some animal studies suggest that EGCG activates gamma amino butyric acid (GABA) A receptors causing sedative and hypnotic effects (Adachi et al 2006, Vignes et al 2006). A number of rat experiments have shown memory improvement in older animals. Improved spatial cognition learning ability in rats was demonstrated after the administration of long-term GTCs (Haque et al 2006). Significant improvement in memory and learning was found in older rats administered with green tea extract over 8 weeks (Kaur et al 2008)

EGCG and other tea polyphenols

Catechins are the most important flavanols in green tea and EGCG is the catechin thought to be the most pharmacologically active phytochemical. EGCG and the other green tea polyphenols have gained world-wide attention because they have multiple mechanisms of action and are extremely safe. So far, research has confirmed they are strongly antioxidant, anticarcinogenic, chemoprotective, antiproliferative, anti-angiogenic and apoptotoic on multiple cancer cell types, antithrombotic, anti-inflammatory, hypolipidaemic, antihypotensive, antidiabetic, thermogenic, antibacterial, antiviral, UV-protective, neuroprotective, neurorescue, anti-amyloidogenic and have iron- and metal-chelating activities.

As a result, there is a lot of work being conducted to determine whether EGCG and green tea can be part of an effective therapeutic strategy for the prevention and treatment of a number of the major diseases affecting the Western world. Conditions currently being studied include cardiovascular disease, cancers, neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and dementia, and diabetes.

CLINICAL USE

Evidence is largely based on epidemiological studies with few clinical studies available.

Cancer prevention

It is still unclear whether green tea consumption reduces the incidence of all cancers or has any effect on mortality; however, studies of individual cancers show some protective effects. Supportive evidence is most consistent for breast and prostate cancers, with some supportive evidence for endometrial cancer and leukaemia and less consistent evidence for gastric cancers.

All cancers

A 2001 prospective study in Japan found no association between green tea consumption and cancer incidence (Nagano et al 2001) whereas a 2003 study using 13-year follow-up data found increased green tea consumption was associated with an apparent delay of cancer onset and death, and all cause deaths (Nakachi et al 2003).

Alternately, the Ohsaki National Health Insurance Cohort study in Japan followed a population of 40,530 Japanese adults and did not find a significant correlation between green tea consumption and reduced mortality due to cancer (Kuriyama et al 2006).

Breast cancer

A meta-analysis of three cohort studies from Japan and one population case control study from the US concluded that green tea consumption reduced the risk of breast cancer (Sun et al 2006). Similar protective effects were observed in a case–control study in China, which found that regular drinking of green tea reduced breast cancer risk (Zhang et al 2007).

Endometrial cancer

Green tea drinking was found to be mildly protective of endometrial cancer risk in a population-based case–control study in China where 995 cases were interviewed. This protective effect might be limited to pre-menopausal women (Gao et al 2005).

Prostate cancer

A case–control study in China with 130 prostate cancer patients found that green tea was protective against prostate cancer with lower risk associated with an increase in the frequency, duration and quantity of green tea consumed (Jian et al 2004). Drinking green tea was also associated with a reduction in the risk of advanced prostate cancer in 49,920 men aged 40–69 years who completed questionnaires over a 10-year period in the Japan Public Health Centre-based Prospective Study. The effect was dose dependent and strongest for men drinking five or more cups/day compared with less than 1 cup/day (Kurahashi et al 2008).

Gastric cancer

A meta-analysis of 14 epidemiological studies found that green tea was not associated with a reduced risk of gastric cancer (Zhou et al 2008). In contrast, in the same year a systematic review of 43 epidemiological studies, four randomised trials and one meta-analysis concluded that green tea consumption may reduce incidence of gastrointestinal cancers but inconsistencies in the evidence meant further long-term clinical trials are required (Liu et al 2008).

Colorectal cancer

A meta-analysis of studies investigating green tea consumption and colorectal cancer risk evaluated eight studies and found that using the available epidemiological data it could not be concluded that green tea was protective (Sun et al 2006). A year later, a large prospective study of 69,710 Chinese women reported regular tea drinking reduced the risk of both colon and rectal cancers (Yang et al 2007).

Liver cancer

According to a placebo-controlled, randomised study, green tea polyphenols may reduce the incidence of hepatocellular carcinoma (HCC) in high-risk patients (Yu et al 2006). The study involved 1209 males, who tested positive for hepatitis B virus and then allocated to the control group or active treatment with green tea polyphenols (two capsules daily of 500 mg). The trial lasted 3 years with a further 2-year follow-up period. Ten cases of HCC were reported in the green tea group and 18 cases in the placebo group.

Leukaemia

Leukaemia risk may be reduced with drinking sufficient amounts of green tea. The protective effect was significant in the 16–29-year age range with higher amounts of green tea consumption; there was no significant relationship to green tea drinking and leukaemia risk in younger people in the 0–15-year age range. These findings were from a population-based study in Taiwan (Kuo et al 2009).

Cancer treatment

Studies have been conducted with various doses of green tea and GTCs in different cancers producing mixed results.

Overall, the current evidence does not support the use of green tea as a cancer treatment; however, there are some exceptions, which suggest an adjunctive role. Green tea increased the survival rate of patients with epithelial ovarian cancer in a cohort of 309 Chinese women (Zhang et al 2004). Most (77.9%) of the women in the treatment group were alive at the 3-year follow-up as compared with 47.9% of the control group.

In a randomised controlled trial (RCT), 90 patients with cervical lesions infected with human papilloma virus were given either a capsule containing 200 mg of (-)-epigallocatechin-3-gallate (EGCG) and/or an ointment containing 200 mg of Polyphenon E to be applied daily (Ahn et al 2003). There was a 69% responder rate when compared with placebo, with the ointment showing the best effects.

Several studies have been conducted in men with established prostate cancer. GTCs may have a role in arresting disease development in prostate cancer according to a double-blind, placebo-controlled study (Bettuzzi et al 2008). Sixty volunteers with high-grade prostate intraepithelial neoplasis (HG-PIN) and therefore at high risk of prostate cancer were treated with GTCs (three capsules of 200 mg/day) or placebo over 12 months. Of the 30 men in the GTC group, only one tumour was diagnosed as opposed to nine cases in the placebo group. The GTC group also scored higher on the quality of life scores, had reduced lower urinary tract symptoms and no side effects were detected (Bettuzzi et al 2006). An update for this trial was undertaken 2 years later to see if the prostate cancer was merely delayed rather than prevented in the green tea group. Half the original subjects (equal numbers from placebo and green tea cohorts) agreed to further investigations which detected one more tumour in the GTC group and two more in the placebo group. These results suggest that GTC given for a year may offer long-term protection within this at-risk group and might be useful as first line preventative therapy

In contrast, a small study testing green tea (6 g/day) in patients with pre-existing androgen independent prostate cancer found little effect on prostate specific antigen (PSA) levels (Jatoi et al 2003). Similar results were obtained in a small study of 19 patients with hormone refractory prostate cancer given a lower dose of 250 mg capsules of green tea twice a day (Choan et al 2005). It is likely that this last study did not use a green tea treatment with sufficient concentrations of catechins.

Cardiovascular protection

Epidemiological studies suggest that green tea consumption is associated with a reduced risk of cardiovascular disease (Maeda et al 2003). A 2000 prospective cohort study of 8552 people in Japan found that those consuming more than 10 cups/day, compared with those consuming fewer than three cups, had a decreased relative risk of death from cardiovascular disease (Nakachi et al 2000). The Ohsaki National Health Insurance Cohort Study was a population-based study in Japan, spanning

11 years (1995–2005) with 40,530 Japanese adults aged 40–79 years. At baseline, no participants had cancer or coronary heart disease. The study identified an inverse association between green tea consumption and mortality due to cardiovascular disease (especially mortality due to stroke) as well as all other causes. A significant protective effect was shown at a dose of five cups or more daily for men and three or more cups daily for women. Overall, the protective effects were greatest for women compared to men (Kuriyama et al 2006). The investigators suggested higher smoking levels in men may have reduced potential benefits in this group (Cheng 2007). A review of the literature looking at green tea and stroke prevention suggested that epidemiological studies in countries where green tea consumption was prevalent showed promising results. Further clinical trials were recommended to confirm the findings (Fraser et al 2007).

Lipid lowering

A meta-analysis evaluating the association between cardiovascular risk and flavonoid-rich nutrients drew from four studies to conclude that green tea reduced LDL cholesterol (between 0.12 and 0.34 mmol/L) (Hooper et al 2008). A significant reduction in LDL cholesterol and triglycerides and marked increase in HDL cholesterol was also found for green tea consumption (400 mg given three times daily) in a double-blind, placebo, RCT of 78 obese women conducted over 12 weeks (Hsu et al 2008). Similar results were obtained in an early cross-sectional study involving 1371 men aged over 40 years (Imai & Nakachi 1995). The study showed that increased green tea consumption was associated with decreased serum concentrations of total cholesterol and triglyceride and an increase in HDL, together with a decrease in LDL and very low density lipoproteins (VLDL) cholesterols.

In contrast, the inclusion of 3 g/day of green tea to a cholesterol lowering diet provided no further lipid lowering effects according to a study of 100 hypercholesterolaemic patients (Bertipaglia de Santana et al 2008). Whilst green tea increased antioxidant potential there was no significant reduction in any cholesterol parameters.

Dental caries and gingivitis

Green tea extract tablets and chewable oral preparations have been investigated for effects on dental plaque formation and gingival health under RCT conditions, overall producing favourable results (Liu & Chi 2000).

A double-blind study investigated the effects of GTCs and polyphenols on the gingiva when used in the form of chewable oral sweets (Krahwinkel & Willershausen 2000). Compared with placebo, the green tea product chewed eight times a day significantly decreased gingival inflammation and improved periodontal structures before the 21-day test period was complete.

Another study investigated Chinese green tea polyphenol tablets for effects on plaque formation in 150 volunteers (Liu & Chi 2000). The randomised, controlled crossover study showed that green tea polyphenol tablets used for 2 weeks were able to reduce the plaque index compared with placebo treatment.

Sunburn protection

More than 150 in vitro and in vivo studies have reported the benefits of green tea for the skin (Hsu 2005). Many mechanisms appear to be responsible; green tea protects against UV and psoralen + ultraviolet A (PUVA)-induced carcinogenesis and DNA damage and is a potent antioxidant, anti-inflammatory, anticarcinogenic and vulnerary (Hsu 2005). Research with human volunteers has found that topical application of green tea to skin half an hour before UV exposure protects against the development of sunburn and epidermal damage (Elmets et al 2001). The effect is dose dependent and strongest for the epigallocatechin gallate and epicatechin gallate polyphenols.

Weight loss

Animal studies have found that green tea consumption reduces food intake, decreases leptin levels and body weight and increases thermogenesis. However, little clinical evidence is available to determine whether similar effects are seen in humans (Sayama et al 2000).

Clinical studies investigating the effects of green tea on weight loss have produced mixed results.

One open study found that a green tea extract AR25 (80% ethanolic dry extract standardised at 25% catechins) taken by moderately obese patients resulted in a 4.6% decrease in body weight and 4.5% decrease in waist circumference after 3 months' treatment (Chantre & Lairon 2002). Both groups lost the same amount of weight and displayed similar metabolic parameters at the end of the study period. An RCT study in Thailand was undertaken over 12 weeks with 60 obese individuals all given a similar diet of three meals a day with 65% carbohydrates, 15% protein and 20% fat. There was no significant difference in weight loss at week 4 but at weeks 8 and 12 weight reduction was significantly greater in the green tea group than the placebo group. The difference in weight loss between the groups was 2.70 kg at 4 weeks, 5.10 kg at 8 weeks and 3.3 kg at 12 weeks. Researchers suggested the effects were due to changes in resting energy expenditure and fat oxidation (Auvichayapat et al 2008). However, two other studies produced negative findings. One double-blind, placebo-controlled parallel trial, with 46 women attempting a weight-loss program over 87 days, showed no difference between the green tea group and the placebo group (Diepvens et al 2005). Another double-blind, placebo, RCT, with 78 obese women, also showed no significant difference in body weight, body mass index (BMI) or waist circumference after taking a green tea extract capsule of 400 mg three times a day for 12 weeks (Hsu et al 2008).

Liver disease

A systematic review of 10 studies showed that increased green tea consumption is associated with a reduced risk of liver disease. The studies were published between the years 1995 and 2005, with

numbers of subjects ranging from 52 to 29,090. Of the 10 studies, four were RCTs, two cohort, one case–control and three cross-sectional studies. Among them, eight studies were conducted in China, one in Japan and the other in the USA. Most of the studies used adjustments such as age, sex, smoking, drinking to control potential confounders and the study periods varied from less than 6 months to more than 6 years. Eight studies yielded statistically significant results showing a protective role of green tea against liver disease whereas two studies only showed a partial tendency. Also, four studies showed a positive association between green tea intake and attenuation of liver disease. When considering the protective effects of green tea against subgroups of liver diseases, it seems that they are more effective in fatty liver disease and liver disorders than in liver cancer as two studies involving liver cancer did not show a significant protective effect (Jin et al 2008). Despite these promising results, more rigorous double-blind studies are still required to confirm the results as the studies used in the review were heterogeneous and differed in the design, outcome, tea dosage and other aspects.

OTHER USES

Green tea has many other uses, based on results of animal or in vitro tests or on the known pharmacological activity of constituents such as tannin and caffeine. Some of these other uses are treatment of diarrhoea, Crohn's disease, dyspepsia and other digestive symptoms, promoting alertness and cognitive performance, reducing symptoms of headache and promoting diuresis.

Colitis

Animal studies have shown anti-inflammatory activity in colitis (Varilek et al 2001, Westphal et al 2008).

Dementia/cognitive impairment

Several in vivo studies have demonstrated memory improvement in older animals for green tea extract and improvements in spatial cognition learning ability after long-term administration of GTCs (Haque et al 2006, Kaur et al 2008). A community-based self-administered questionnaire of 1003 Japanese geriatric people found that greater ingestion of green tea was associated with lower cognitive impairment (Kuriyama et al 2006). Green tea intake was significantly associated with better cognitive performance in a 2-year follow-up study of Japanese elderly (Hasegawa et al 2005).

Beta-thalassaemia

An in vitro research shows green tea chelates iron which should be investigated further to determine whether there are benefits in the management of iron overload in conditions such as beta-thalassaemia (Srichairatanakool et al 2006).

Renal failure

Green tea extract blocks the development of cardiac hypertrophy in experimental renal failure and reduces oxidative stress, according to the results of investigation with animal models (Priyadarshi et al 2003, Yokozawa et al 1996).

Urinary stones

Two in vivo and in vitro studies have shown that green tea's antioxidant action may inhibit kidney stone formation (Itoh et al 2005, Jeong et al 2006).

Diabetes

Animal studies have identified that green tea polyphenols reduce serum glucose levels and improve kidney function in diabetes (Sabu et al 2002, Rhee et al 2002). Other in vivo studies have confirmed that green tea may have a therapeutic use in diabetes (Juskiewicz et al 2008). However, one animal study found that fasting blood glucose levels were increased in diabetic rats fed green tea (Islam & Choi 2007). Evidence from human trials has been contradictory. One double-blind RCT with 49 individuals with type 2 diabetes mellitus found no significant hypoglycaemic effects for green tea given at 375 mg or 750 mg/day (MacKenzie et al 2007). Another RCT of 66 diabetic patients found 500 mg/day of green tea polyphenols had no clear effect on blood glucose or insulin resistance markers (Fukino et al 2005). An epidemiological study of 542 men and women, aged over 65 years, from the Mediterranean islands found that tea consumption (green and black) was associated with reduced levels of fasting glucose but this was only in the non-obese subjects (Polychronopoulos et al 2008).

Genital warts

A number of recent trials have shown good effectivity for a topical treatment (Polyphenon E by Medigene EU) containing a fixed amount of GTCs in the treatment of genital warts. The product is marketed as Veregen™ in the USA.

Healing of genital warts occurred in 54.9% of patients using Polyphenon E ointment compared with 35.4% of patients receiving placebo in three placebo clinical studies of 1400 patients (Gross 2008). Another trial with the same Polyphenon E topical treatment evaluated 503 patients, with external genital and perianal warts, who were randomised to be treated with a 15% or 10% ointment or a placebo. Treatment was applied three times a day for up to 16 weeks. After follow-up, 12 weeks later, 53% of patients with the 15% strength ointment had complete clearance, 51% for the 10% ointment and 37% for the control vehicle. A greater number of women experienced total clearance of all warts (with the Polyphenon E treatment compared to men, 60% compared to 45% [Stockfleth et al 2008]) Another double-blind, placebo, RCT, with 502 patients with genital and perianal warts used a topical treatment of sinecatechins (a defined green tea extract), which was found to be effective and well tolerated. The findings were significant at weeks 4, 6 and subsequent visits over the 16-week trial. Complete clearance of warts was obtained in 57% of patients compared with only 33% with the control group (Tatti et al 2008).

DOSAGE RANGE

The dose varies depending on the indication it is being used for. Some research suggests 8–10 cups of green tea/day are required for effects whereas others indicate only 3–5 cups of green tea/day are required. It is likely the dose also depends on the quality of the green tea and the concentration of GTCs in the preparation.

- For external genital and perianal warts: Polyphenon E 15% strength ointment applied three times daily.
- For reduced risk of cancers: five or more cups daily.
- For cardiovascular disease protection: 3–10 cups daily.

ADVERSE REACTIONS

Due to the caffeine content of the herb, CNS stimulation and diuresis are possible when consumed in large amounts.

One clinical study found an absence of any severe adverse effects when 15 green tea tablets were taken daily (2.25 g green tea extracts, 337.5 mg EGCG and 135 mg caffeine) for 6 months (Fujiki et al 1999). One trial with high-dose green tea (600 mg/day) reported adverse effects in 69% of the patients with a range of adverse effects including insomnia, fatigue, nausea, vomiting, diarrhoea, abdominal pain and confusion (Jatoi et al 2003).

SIGNIFICANT INTERACTIONS

Controlled studies are not available for green tea, so interactions are speculative and based on evidence of pharmacological activity. Therefore, clinical significance is unknown.

Anticoagulants

Antagonistic interaction — a case of excessive consumption (2.25–4.5 L of green tea/day) was reported to inhibit warfarin activity and decrease the international normalised ratio (INR) (Taylor & Wilt 1999). Exercise caution with intake of large quantities of green tea.

Hypoglycaemic agents

Caffeine-containing beverages can increase blood sugar levels when used in sufficient quantity (200 mg of caffeine); however, hypoglycaemic activity has been reported for green tea, which could theoretically negate this effect (Ulbricht & Basch 2005) — the outcome of this combination is uncertain, therefore observe patient.

Iron

Tannins found in herbs such as *Camellia sinensis* can bind to iron and reduce its absorption — separate doses by at least 2 hours. Protein and iron have also been found to interact with tea polyphenols and decrease their antioxidant effects in vitro (Alexandropoulou et al 2006). The clinical significance of this is as yet unknown.

CNS stimulants

Based on the caffeine content of the herb, high intakes of green tea can theoretically increase the CNS stimulation effects of drugs such as nicotine and beta-adrenergic agonists (e.g. salbutamol); however, the clinical significance of this is unknown — observe patient.

CNS depressants

Based on the caffeine content of the herb, high intakes of green tea can theoretically decrease the CNS depressant effects of drugs such as benzodiazepines; however, the clinical significance of this is unknown — observe patient.

Bortezomib (BZM) and other boronic acid-based proteasome inhibitors

EGCG was tested in vitro and in vivo to investigate whether combining it with the proteasome inhibitor BZM, commonly used in the treatment of multiple myeloma, would result in an increase in the drugs antitumour activity (Golden et al 2009). Green tea extract almost completely blocked the effects of BZM both in vitro and in vivo — avoid.

Diuretics

Based on the caffeine content of the herb, high intakes of green tea can theoretically increase the diuretic effects of drugs such as frusemide; however, the clinical significance of this is unknown — observe patient.

Drugs metabolised by CYP1A2

The inhibitory effect of caffeine on CYP1A2 may cause other interactions, but this is speculative for green tea. A small trial with 42 volunteers giving 800 mg of green tea a day suggested that drugs metabolised by the CYP enzymes were unlikely to be significantly affected (Chow et al 2006).

CONTRAINDICATIONS AND PRECAUTIONS

Excessive intake will increase the likelihood of adverse effects due to the caffeine content and therefore is not recommended for people with hypertension, cardiac arrhythmias, severe liver disease, anxiety disorders or insomnia.

PREGNANCY USE

Usual dietary intakes appear safe; however, excessive use is not recommended due to the caffeine content of green tea.

PATIENTS' FAQs

What will this herb do for me?

Green tea has strong antioxidant effects and some population studies suggest that regular consumption may reduce the risk of cancer and cardiovascular disease. Early research has found it may be useful for sunburn protection, reducing dental plaque formation, colitis, diabetes, renal disease, improving memory and cognition and as an antiseptic. However, further research is required.

When will it start to work?

This will depend on the reason it is being used. Preventative health benefits are likely to take several years of regular daily tea consumption. Effects on

PRACTICE POINTS/PATIENT COUNSELLING

- Green tea is made from the same plant as black tea, but it contains greater amounts of polyphenols and generally less caffeine.
- Green tea has been found to have significant antioxidant activity and protects against sunburn when applied topically.
- It has antibacterial activity and is used in oral preparations to reduce plaque and improve gingival health.
- Several in vitro and animal studies have shown anticarcinogenic activity for a range of cancers and some epidemiological evidence further suggests cancer protective effects may occur; however, further research is required. Patients with a high risk of prostate or liver cancer (due to hepatitis B) may benefit from regular green tea drinking.
- Epidemiological evidence suggests green tea may reduce cardiovascular disease especially stroke risk and LDL cholesterol.
- Preliminary evidence from animal studies has shown that it increases thermogenesis, decreases appetite, reduces inflammation in colitis, reduces glucose levels in diabetes, may be useful in renal failure, and has potential to improve cognitive function in the elderly and be used in Alzheimer's and Parkinson's diseases.
- It is not known whether the use will promote weight loss in humans as research results are inconsistent.
- A proprietary ointment made from a fixed concentration of GTCs is effective in the treatment of genital warts.

oral health care appear to develop more quickly, within 2 weeks.

Are there any safety issues?

Research suggests that green tea is a safe substance when used in usual dietary doses, but excessive consumption may produce side effects, chiefly because of the caffeine content.

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Guarana

HISTORICAL NOTE Guarana has been used by the Amazonian Indians of South America for centuries to enhance energy levels, suppress appetite, increase libido and protect them from malaria. More recently, hot guarana beverages have been adopted by the greater population as a tonic to enhance wellbeing, in much the same way coffee is drunk in Australia.

COMMON NAME
Guarana

OTHER NAMES
Brazilian cocoa, guarana gum, guarana paste, quarana, quarane, uabano, uaranzeiro, zoom

BOTANICAL NAME/FAMILY
Paullinia cupana (family Sapindaceae)

PLANT PART USED
Seeds

CHEMICAL COMPONENTS
Guarana seeds are a rich source of caffeine, containing 3–6% on a dry weight basis (Saldana et al 2002). Other major compounds include theobromine, theophylline, tannins, resins, protein, fat and saponins (Duke 2003).

MAIN ACTIONS
A review of the scientific literature reveals that guarana itself has only recently been the subject of clinical studies. As such, studies pertaining to caffeine are sometimes used to explain the herb's action, an approach that presupposes the other constituents are either inactive or of such weak effect they need not be recognised. Although this approach is convenient and provides us with some understanding of the herb's pharmacological effects, the results of four recent clinical studies suggest that guarana's effects on cognitive function are due to more than its caffeine content. It has also been suggested that the effects of guarana are longer lasting than caffeine, possibly due to the saponin and tannin content (Babu et al 2008).

CNS stimulant
Although guarana has not been clinically investigated for its effects on the CNS, there is a great deal of evidence to show that caffeine is an antagonist of the adenosine receptor, which produces a net increase in CNS activity because the inhibitory action of adenosine is blocked (Smith 2002). This results in the release of a variety of neurotransmitters (e.g. noradrenaline, acetylcholine, dopamine, and the GABA/benzodiazepine system).

OTHER ACTIONS

Inhibits platelet aggregation
Guarana inhibits platelet aggregation both in vitro and in vivo (Bydlowski et al 1988, 1991). Decreased thromboxane synthesis may in part explain this activity.

Gastric effects
Guarana may increase gastric acid secretion and delay gastric emptying. This has been demonstrated in a clinical study using a herbal combination known as 'YGD', which contains yerba mate (leaves of *Ilex paraguayensis*), guarana (seeds of *Paullinia cupana*) and damiana (leaves of *Turnera diffusa* var. *aphrodisiaca*) (Andersen & Fogh 2001). Whether stand-alone treatment with guarana will produce similar effects is unknown.

Chemoprotective
Guarana has been shown to be chemoprotective in a mouse hepatocarcinogenesis model (Fukumasu et al 2005). The herb was found to reduce the cellular proliferation of preneoplastic cells. It has also been demonstrated that guarana is protective against chemically induced DNA damage in mouse liver. This effect was attributed to the tannin content of the herb (Fukumasu et al 2006). A later mouse experiment observed a decrease in proliferation and an increase in apoptosis of melanoma lung metastases resulting in a reduction in tumour size (Fukumasu et al 2008).

Antibacterial
In vitro data has demonstrated the antibacterial and antioxidant effects of the ethanolic extract of guarana, thought to be due to the phenolic compounds (Basile et al 2005). Guarana was shown to be effective against many pathogens of the digestive tract including *Escherichia coli*, *Salmonella typhimurium* and *Staphylococcus aureus.* This adds weight to the traditional use of guarana for diarrhoea. More recently in vitro research has demonstrated antibacterial activity against *Streptococcus mutans* which could have applications in preventing dental plaque (Yamaguti-Sasaki et al 2007). Antimicrobial activity was further confirmed in vitro when testing guarana seed extracts against food-borne fungi and bacteria. This may have applications in food preservation (Majhenic et al 2007).

Antioxidant
A strong antioxidant activity has been demonstrated in vitro for guarana seeds (Majhenic et al 2007).

Other actions relating to caffeine content
Although these have not been tested for guarana directly, the caffeine content, which is well absorbed from the herb, may cause mild dilation of the blood vessels; an increase in blood pressure, renin and catecholamine release, urine output, metabolic rate, lipolysis, respiration and intestinal peristalsis; and inhibition of CYP1A2. Caffeine also possesses thermogenic properties (Astrup 2000).

CLINICAL USE

Mood enhancing

For several years anecdotal evidence has suggested that guarana produces similar effects to caffeine on subjective feelings of wellbeing, energy, motivation and self-confidence (Mumford et al 1994). Tests with animal models indicate guarana exerts a mild antidepressant effect thereby providing some support for the observed mood elevating effects (Campos et al 2005, Otobone et al 2007).

Mood elevation was further demonstrated in a recent double blind, placebo-controlled, multi-dose clinical study involving 26 volunteers which tested a low caffeine containing guarana extract (PC-102) (Haskell et al 2007). Four strengths were investigated (37.5 mg, 75 mg, 150 mg and 300 mg). Treatment at each dose level produced a significant effect on mood. As there were low levels of caffeine measured in the guarana extract, mood elevation cannot be explained by the caffeine content alone.

Enhanced cognitive function and alertness

At least six clinical studies have been conducted to investigate whether guarana affects cognitive function, producing mixed results thus far. Four double-blind studies report that guarana has significant effects on cognitive function and provides evidence that these effects are not just mediated by the herb's caffeine content (Haskell et al 2005, Haskell et al 2007, Kennedy et al 2004, Kennedy et al 2008). In contrast, two double-blind studies failed to identify significant effects for guarana on cognitive function (Galduroz & Carlini 1994, 1996).

One double-blind, placebo-controlled study assessed the effects of four different doses of guarana (37.5 mg, 75 mg, 150 mg, and 300 mg) in 22 subjects (Haskell et al 2005). Cognitive performance and mood were assessed at baseline and again 1, 3 and 6 hours after each dose using the Cognitive Drug Research computerised assessment battery, serial subtraction tasks, a sentence verification task and visual analogue mood scales. All doses improved picture and word recognition, results on the Bond–Lader visual analogue scales and caffeine research visual analogue scales showing improvements in alertness and reduced ratings of headache. The two lower doses produced better results than the two higher doses, which were associated with impaired accuracy of choice reaction and one of the subtraction tests. Several observations suggest that these effects were not due to caffeine alone. Firstly, effects were still apparent 6 hours after administration and secondly, better results were obtained with a dose of 37.5 mg than 300 mg with a caffeine content of less than 5 mg in the lowest dose. The study was replicated 2 years later, with a double-blind, counterbalanced, placebo-controlled study (Haskell et al 2007). In this study, 26 participants were given the same four doses of a standardised guarana extract. All doses improved mood however cognitive improvements were greatest for the two lower doses, with the 75 mg dose most effective. As there was only 9 mg of caffeine in this dose it is unlikely that the effects can be attributed solely to the caffeine content.

Another double-blind, placebo controlled study investigated the effects of a single dose of guarana (75 mg) on cognition, in combination with and in comparison to ginseng (*Panax ginseng* 200 mg) in 28 healthy volunteers (Kennedy et al 2004). Guarana was shown to produce comparable effects to ginseng in improved task performance with all three treatments better than placebo. However, guarana was superior to ginseng in improving the speed of performed tasks. Once again, given the low caffeine content (9 mg) of the guarana extract used in this study, the effects are unlikely to be attributable to its caffeine content alone, particularly as the dose was shown to be as effective as a 16-fold dose of pure caffeine. A later double-blind, randomised, placebo-controlled study of 129 adults tested a multi-vitamin and mineral supplement with added guarana (Berocca Boost with 222 mg guarana and 40 mg caffeine) and found it supported the previous findings that guarana improves cognitive performance. A single dose of the supplement also reduced mental fatigue after sustained mental effort (Kennedy et al 2008).

Two other randomised, double-blind studies have investigated the effects of guarana on cognitive function (Galduroz & Carlini 1994, 1996). One study involving 45 healthy elderly volunteers found that guarana treatment was ineffective (Galduroz & Carlini 1996), which confirmed the findings of a previous study conducted by the same authors (Galduroz & Carlini 1994). Studies in some animal models have produced positive results for both single-dose and long-term administration of guarana, observing a positive effect on memory acquisition and memory maintenance (Espinola et al 1997).

Ergogenic aid

Guarana is also used as an ergogenic aid by some athletes, most likely because caffeine and theophylline have been used in this way, to improve performance in training and competition (Graham 2001). No human studies testing guarana for effects on physical performance could be located. Referring to caffeine studies, it appears that ergogenic effects are observed under some conditions but not under others (Doherty et al 2002, Hunter et al 2002, Ryu et al 2001). Testing guarana in several animal models has also produced contradictory results. Significant increases in physical capacity have been observed with a dose of 0.3 mg/mL of a guarana suspension after 100 and 200 days' treatment. However, the same effect was not seen with a concentration of 3.0 mg/mL nor with a solution of caffeine 0.1 mg/mL (Espinola et al 1997).

Appetite suppressant and weight loss aid

Weight-loss products often contain guarana, in the belief that it suppresses appetite and may have thermogenic and diuretic activities. An animal study designed to evaluate the effects of guarana and decaffeinated guarana found that only the caffeinated herb was effective for weight loss (Lima et al 2005).

To date, most clinical studies have investigated the effects of guarana in combination with other herbs.

In combination

A double-blind RCT testing a combination of yerba mate (leaves of *Ilex paraguayensis*), guarana (seeds of *Paullinia cupana*) and damiana (leaves of *Turnera diffusa* var. *aphrodisiaca*) found that the preparation significantly delayed gastric emptying, reduced the time to perceived gastric fullness and induced significant weight loss over 45 days in overweight patients (Andersen & Fogh 2001).The same herbal combination (Zotrim) was tested in an open study of 73 overweight health professionals, over six weeks. Active treatment resulted in a significant reduction in self-reported weight and waist and hip measurements, and increased satiety after meals. Significant weight loss was reported by 22% of volunteers.

Another randomised double-blind placebo-controlled trial evaluated the effects of guarana in combination with Ma Huang (*Ephedra* spp) and concluded that the formula was effective for weight loss in overweight men after 8 weeks of treatment (Boozer et al 2001). A more recent double-blind, placebo-controlled, randomised study tested a multi-component herbal combination containing extracts from asparagus, green tea, black tea, guarana, mate, kidney beans, Garcinia cambogia and chromium yeast and found that over a 12-week period there was a significant change in the Body Composition Improvement Index and decreased body fat compared to placebo (Opala et al 2006). The formula was more effective for those participants who were undertaking an exercise program at the same time than for those who remained sedentary.

A short-lived increase in metabolic rate was observed in a small double-blind, placebo-controlled, crossover study of 16 healthy subjects (Roberts et al 2005). A product containing primarily black tea (*Camellia sinensis*) and guarana extract providing 36% caffeine (plus vitamin C and some other trace nutrients and herbs) increased metabolic rate after 1 hour with no significant difference at the 2 hour check.

Although encouraging, the effects of guarana as a stand-alone treatment need to be confirmed.

OTHER USES

Traditionally, guarana has been used as an aphrodisiac, a treatment for diarrhoea, a diuretic and as a beverage in some cultures.

DOSAGE RANGE

According to clinical trials

- Cognition, alertness and mood: doses between 37.5 and 75 mg are sufficient to provide effects for at least 6 hours.
- For other indications, guarana has not been significantly researched. Based on its caffeine content, it is advised that doses should not exceed that amount that will provide approximately 250 mg of caffeine daily. This is equivalent to 2.5–4 g guarana/day, depending on the caffeine content of the preparation.

TOXICITY

Animal tests have shown that high doses of 1000–2000 mg/kg (intraperitoneal and oral) do not induce significant alterations in parameters for toxicological screening, suggesting an absence of toxicity (Mattei et al 1998).

ADVERSE REACTIONS

Due to a lack of clinical studies testing guarana as a stand-alone treatment, it is difficult to determine what adverse reactions may exist.

Based on caffeine content, the following adverse effects may theoretically occur at high doses: agitation, tremor, anxiety, restlessness, headache, seizures, hypertension, tachycardia and premature ventricular contractions, diarrhoea, gastrointestinal cramping, nausea and vomiting and diuresis.

SIGNIFICANT INTERACTIONS

Controlled studies are not available, therefore interactions are theoretical and based on evidence of pharmacological activity with uncertain clinical significance.

Clinical note — Popular energy drinks and caffeine content

Adolescents in particular are high consumers of energy drinks with a reported 30% of teens in the US using these drinks in 2006 (Babu et al 2008). They often contain a mixture of caffeine, guarana, taurine, other herbs and vitamins. According to product labels and websites, the following drinks contain varying amounts of caffeine:

Coca Cola	34 mg per 355 mL can
Diet Coke	45.6 mg per 355 mL
Diet Pepsi	36 mg per 355 mL
Diet Pepsi Max	69 mg per 355 mL
Red Bull	80 mg per can
Mother	80 mg per 250 mL
V	78 mg per 250 mL
Brewed coffee	100 mg per cup

A large intake of these drinks can produce adverse effects based on their caffeine content such as headache, agitation, insomnia, anxiety, tremor, restlessness, seizures, tachycardia, and nausea and other gastrointestinal disturbances. Four independent cases associating high consumption of energy drinks with seizures have been reported (Iyadurai & Chung 2007). It is possible that these four individuals may have been genetically susceptible and the high consumption of these drinks may have reduced the seizure threshold. It has been found that caffeine excess lowers the threshold to seizures so the caffeine content of the energy drink is the most likely cause. A prudent suggestion would be to avoid a high intake of these drinks. There has been one reported case of intractable ventricular fibrillation in a young woman with a pre-existing mitral valve prolapse. This occurred after consuming an energy drink with guarana and high caffeine content (Cannon et al 2001).

Clinical note — Is caffeine safe in pregnancy?

There have been numerous studies investigating the effects of caffeine in pregnancy with inconsistent results. A meta-analysis of 32 case-control or cohort-design studies found that there was a small statistically significant increase in the risk of spontaneous abortion and of low birth weight babies where the pregnant mother consumed more than 150 mg of caffeine per day (equivalent to about 1.5 cups of freshly brewed coffee) (Fernandes et al 1998). Confounders such as maternal age, smoking and alcohol use could not be excluded. More recent studies have produced varying results with one cohort study in Denmark concluding that high levels of coffee consumption were associated with a higher risk of fetal death, especially after 20 weeks (Bech et al 2005). A population-based case-control study in Uruguay also showed a significantly increased risk of fetal death when more than 300 mg caffeine per day is consumed (Matijasevich et al 2006). An increased risk of repeated miscarriage with high caffeine intake was reported in a Swedish study (George et al 2006) and a more recent study found an increased miscarriage risk even allowing for pregnancy-related symptoms (Weng et al 2008). The risk of small-for-gestational-age (SGA), especially for boys, was nearly doubled for mothers with high rather than low caffeine intake in the third trimester (Vik et al 2003).

In contradiction to these findings other studies showed caffeine consumption was unlikely to be a major risk factor for SGA or low birthweight babies (Infante-Rivard 2007), and a systematic review showed no association between moderate caffeine consumption and fetal growth (Pacheco et al 2007). Another large prospective study confirmed that there was no clinical importance demonstrated looking at fetal growth except for women consuming 600 mg caffeine daily (Bracken et al 2003).

It therefore seems prudent that caffeine intake should be avoided or limited throughout pregnancy and that the caffeine content of guarana products should be checked before use.

CNS stimulants

Additive stimulant activity is theoretically possible, so use with caution.

CNS sedatives

Antagonistic effects are theoretically possible due to the herb's CNS stimulant activity. However, one in vivo study found no interaction with pentobarbital. Observe patients taking this combination.

Diuretics

Additive diuretic effects are theoretically possible — use this combination with caution.

Anticoagulants

Increased bleeding is theoretically possible, as in vitro and in vivo research has identified antiplatelet activity for guarana. Use this combination with caution.

Antiplatelet drugs

Additive effects are theoretically possible as in vitro and in vivo research has identified antiplatelet activity for guarana. Observe patients taking this combination.

Digoxin

Long-term use of high-dose supplements can result in reduced potassium levels, which lowers the threshold for drug toxicity. Avoid long-term use of high-dose guarana preparations.

Drugs metabolised by CYP1A2

The inhibitory effect of caffeine on CYP1A2 may cause other interactions, but this is highly speculative for guarana.

CONTRAINDICATIONS AND PRECAUTIONS

Contraindicated in moderate to severe hypertension and cardiac arrhythmias.

Use with caution in anxiety states, hypertension, diabetes, gastric ulcers and chronic headache. Adverse reactions may be dose dependent. Suspend use of concentrated extracts 1 week before major surgery.

Under the World Anti-Doping Code 2007 Prohibited List caffeine is not classified as a prohibited stimulant, unless specified by particular sports. Therefore athletes are recommended to check with their own sports federation about the status of caffeine containing substances.

PREGNANCY USE

The use of caffeine-containing preparations should be limited during pregnancy and breastfeeding as it has the ability to cross the placenta and can be found in breast milk. Caffeine clearance is also delayed in the second and third trimesters with the half-life of caffeine increasing to 10.5 hours from 2.5-4.5 hours in a non-pregnant woman. It also appears that the fetus has a reduced capacity to metabolise caffeine.

PRACTICE POINTS/PATIENT COUNSELLING

- Guarana has mild CNS stimulant properties and increases alertness, cognitive function and mood.
- Current evidence is inconclusive as to whether guarana also enhances physical stamina.
- It has been used in combination with other herbs as a weight-loss aid with some degree of success. However, it is unknown what role guarana played in achieving these results.
- In some sensitive individuals, guarana may produce CNS stimulant-related side effects, such as elevated heart rate and blood pressure, tremor, restlessness and excitability.

PATIENTS' FAQs

What will this herb do for me?

Guarana is a herbal stimulant that increases alertness, cognitive function and possibly mood.

How quickly does it start working?

Effects are expected 1–2 hours after ingestion, although this will vary depending on the individual and the current level of wakefulness.

Are there any safety issues to be aware of?

Used in small amounts, it is likely to have a degree of stimulant activity and decrease fatigue; however, as with all stimulants, excessive use or long-term use can be detrimental to health. Guarana should be used with caution in people with hypertension, anxiety states, gastric ulcers, diabetes and some types of cardiovascular disease. It may also interact with a variety of medicines and therefore it is recommended to consult your healthcare professional if you are currently taking pharmaceutical medication.

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Gymnema sylvestre

HISTORICAL NOTE Gymnema has been called the sugar destroyer because the leaf suppresses the ability to taste sweet on the tongue. It has been used to treat diabetes, as well as to aid metabolic control when combined with other herbal medicines.

COMMON NAME
Gymnema

OTHER NAMES
Asclepias geminate, gurmar (sugar destroyer), gemnema melicida, gokhru, gulrmaro, gurmar, gurmara, gurmarbooti, kar-e-khask, kharak, merasingi, meshasringi, masabedda, *Periploca sylvestris*, sirukurinjan

BOTANICAL NAME/FAMILY
Gymnema sylvestre (family Asclepiadaceae)

PLANT PART USED
Leaf

CHEMICAL COMPONENTS
Gymnema contains gymnemasaponins, gymnemasides, gymnemic acids and gypenosides (Duke 2003), oleanane-type triterpenic acid (Peng et al 2005) and flavonol glycosides (Liu et al 2004), as well as a range of nutrients, including ascorbic acid, beta-carotene, chromium, iron, magnesium and potassium. The main active chemical components appear to be the gymnemic acids, gymnemasaponins and the polypeptide gurmarin.

MAIN ACTIONS

Sweet-taste suppression
The constituent, gymnemic acid, inhibits the ability to taste sweetness in animal models (Fushiki et al 1992, Harada & Kasahara 2000, Kurihara 1969, 1992) and humans (Frank et al 1992). In humans, the administration of 5 mmol/L gurmarin to the tongue raised the threshold ability to taste sucrose from 0.01 mol/L to 1 mol/L for several hours. It is suggested that gurmarin acts on the apical side of the taste cell, possibly by binding to the sweet taste receptor protein (Miyasaka & Imoto 1995).

Antidiabetic
Gymnema's antidiabetic activity appears to be due to a combination of mechanisms, including reduction of intestinal absorption of glucose (Shimizu et al 2001), inhibition of active glucose transport in the small intestine (Yoshioka 1986), suppression of glucose-mediated release of gastric inhibitory peptide (Fushiki et al 1992), increased activity of the enzymes responsible for glucose uptake and use (Shanmugasundaram et al 1983), stimulation of insulin secretion (Persaud et al 1999, Sugihara et al 2000) and increasing the number of islets of Langerhans and number of pancreatic beta cells (Prakash et al 1986, Shanmugasundaram et al 1990). *Gymnema montanum* (a related species) has also been shown to have antidiabetic, antiperoxidative and antioxidant effects in diabetic rats (Ananthan et al 2003) and antioxidant activity evident in the liver, kidney (Ananthan et al 2004) and brain tissues (Ramkumar et al 2004).

Animal studies suggest that gymnema will reduce blood sugar levels in response to a glucose load in streptozotocin-induced mildly diabetic rats (Okabayashi et al 1990) and alloxan-induced diabetic rats (Shanmugasundaram et al 1983, Srivastava et al 1985), but will not affect blood sugar levels in normal or spontaneously hypertensive rats (Preuss et al 1998). Gymnema extract has been found to return blood sugar and insulin levels to normal in streptozotocin-induced diabetic rats after 20–60 days and to double the number of pancreatic islet and beta cells (Shanmugasundaram et al 1990), as well as maintain stable blood glucose levels in rats given beryllium nitrate (Prakash et al 1986). A recent experimental rat model using streptozotocin to induce type 1 diabetes found that a standardised extract of gymnema, containing 70% of gymnemic acids, produced a significant decrease in blood sugar levels progressing for each of the 3 weeks of the experiment (Jain 2006).

There are currently two negative studies. One study using a dose of 120 mg/kg/day oral gymnema did not find improvements in insulin resistance in insulin-resistant, streptozotocin-induced diabetic rats (Tominaga et al 1995) and the other study, from Brazil using dried powdered leaves of gymnema, found no effect on blood glucose, body weight or food or water consumption in non-diabetic and alloxan-diabetic rats (Galletto et al 2004).

Gymnemic acids have demonstrated hypoglycaemic activity in dexamethasone-induced hyperglycaemic mice (Gholap & Kar 2005) and gymnema, together with other Ayurvedic herbs, has been shown to have hypoglycaemic activity in streptozotocin-induced diabetic mice (Mutalik et al 2005) and rats (Babu & Prince 2004). Gymnema has also been shown to protect the lens against sugar-induced cataract by multiple mechanisms (Moghaddam et al 2005) and protect against the adverse effects of lipid peroxidation on brain and retinal cholinesterases, suggesting a use in preventing the cholinergic neural and retinal complications of hyperglycaemia in diabetes (Ramkumar et al 2005).

Used in combination
A combination of gymnema, *Acacia catechu* and *Pterocarpus marsupium* was found to significantly elevate serum insulin levels in an animal model (Wadood et al 2007). The effect was thought to be due to beta cell regeneration. A polyformula of 18 herbs (Diabegon), including gymnema, was administered to rats resulting in improvement in insulin resistance and

dyslipidaemia (Yadav et al 2007). Another polyherbal formula (Diakyur) also demonstrated significant hypoglycaemic activity and antilipidperoxidative effect (Joshi et al 2007). Whilst these studies demonstrate the success of these specific herbal formulas, it is unclear what role gymnema had in producing these results.

Reduces cholesterol levels

Gymnema extract reduces fat digestibility and increases faecal excretion of cholesterol, neutral sterols and acid steroids, as well as reducing serum cholesterol and triglyceride levels, according to two animal studies (Nakamura et al 1999, Shigematsu et al 2001). Nakamura et al also found that oral administration of gymnema decreased body weight and food intake.

Antimicrobial, antibacterial and antiviral

The ethanolic extract of *Gymnema sylvestre* leaves demonstrated antimicrobial activity against *Bacillus pumilis*, *B. subtilis*, *Pseudomonas aeruginosa* and *Staphylococcus aureus* (Satdive et al 2003). This finding was confirmed in a later in vitro study which found that gymnemic acid extract exerted strong antibacterial activity against *Bacillus subtilis*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Escherichia coli* and *Salmonella typhi* (Poonkothai et al 2005). Antiviral activity has also been reported (Porchezhian & Dobriyal 2003). A larvicidal effect has also been demonstrated for a 5% concentration of aqueous extract of *Gymnema sylvestre* leaves against *Culex quinquefasciatus* larvae (Gopiesh 2007). The treatment was 100% effective.

OTHER ACTIONS

Gymnema has been found to contain an ATPase inhibitor, which has been shown to block the effect of ATPase from snake venom (Manjunatha & Veerabasappa 1982). According to one animal study, oral administration of gymnema reduces body weight and food intake (Nakamura et al 1999). A significant anti-inflammatory activity was discovered for an aqueous extract of gymnema leaves, which was comparable to that of the drug phenylbutazone in a carrageenan-induced paw oedema animal model (Malik 2008).

CLINICAL USE

Sweet-taste suppression and weight loss

A controlled trial of normal volunteers found that an aqueous gymnema extract with concentrated gymnemic acid reduced sweetness perception by 50%, resulting in reduced caloric consumption 1.5 hours after the sweetness-numbing effect stopped (Brala & Hagen 1983). This result supports the findings of animal studies. In a 6-week randomised, double-blind, placebo-controlled study, a multiherbal formula that included gymnema was found to significantly reduce body weight and fat loss in obese adults after 6 weeks (Woodgate & Conquer 2003); however, the role of gymnema in achieving these results is unknown. A double-blind, placebo-controlled, RCT compared (−)-hydroxycitric acid (HCA-SX) with HCA plus a combination of chromium and *Gymnema sylvestre* extract. In this study, a group of 29 volunteers, in the obese BMI range, were divided into three groups and given the supplements or placebo for 8 weeks and all subjects were provided with a 2000 kcal diet per day and a supervised 30-minute walk for 5 days each week. The study combined data from two previous double-blind, placebo-controlled RCTs and reported that both the HCA-SX group and, to a greater degree, the group with the added chromium and gymnema experienced weight loss, decreased appetite, improvement in blood lipids, higher serum leptin and serotonin levels plus an increase in fat oxidation (Preuss et al 2005).

Type 1 and type 2 diabetes

Orally, gymnema leaf is used to treat both type 1 and type 2 diabetes and hyperglycaemia. There are two clinical trials that suggest that gymnema may be useful in reducing blood glucose levels in both type 1 and type 2 diabetes. In one study, the ability of the GS4 extract (400 mg/day) to supplement the use of conventional oral hypoglycaemic agents (glibenclamide or tolbutamide) was studied in 22 patients with type 2 diabetes over 18–20 months. Treatment resulted in a significant reduction in fasting blood glucose (174 ± 7 vs 124 ± 5 mg/dL), HbA_{1c} (11.91 ± 0.3 vs 8.48 ± 0.13%) and glycosylated plasma protein levels (3.74 ± 0.07 vs 2.46 ± 0.05 microgram hexose/mg protein) and raised insulin levels, whereas no changes were observed in the control group. This allowed for a decrease in conventional drug dosage and in five cases, blood glucose homeostasis was maintained with GS4 alone, suggesting that beta-cell function may have been restored (Baskaran et al 1990). In a second study, 27 patients with type 2 diabetes were treated with 400 mg of an aqueous extract of gymnema in addition to insulin. Insulin requirements were reduced, as were fasting blood sugar levels, HbA_{1c}, glycosylated plasma protein levels and serum lipids (Shanmugasundaram et al 1990).

A small, double-blind, randomised, placebo-controlled trial of a multiherbal Ayurvedic formula containing gymnema showed significantly improved glucose control and reduced HbA_{1c} levels in patients with type 2 diabetes within the 3-month test period (Hsia et al 2004).

A systematic review only found two randomised controlled trials with a mono-preparation of *Gymnema sylvestre* and both were open-label comparative studies so no statistical summary was conducted. The review's findings were limited by the lack of rigorous trials but suggested that gymnema may have a combination of actions that can assist with diabetic complications as well as its aetiology — these effects include anti-inflammatory, weight loss and improving pancreatic beta cell function. As there is no other single drug with such a wide range of actions, gymnema has potential to treat the disease (Leach 2007).

In the light of this comprehensive review of the literature, it seems that gymnema has shown great potential, in trials to date, as a diabetic herbal medication, but more rigorous, well-designed trials are warranted.

Clinical note — Herbs and diabetes
Diabetes has been recognised since ancient times, and as early as 700–200 BC two types of diabetes were recorded in India, one of which was diet related and the other was described as genetic. Diabetes has also been recognised in China for thousands of years, where it is attributed to yin deficiency and treated with an integrated approach that involves more than lowering blood glucose. At least 30 different herbal medicines are used in the management of diabetes and its complications, with several of these having outstanding beneficial potential.

Hypercholesterolaemia and hypertriglyceridaemia

Short-term animal studies have shown that gymnema extracts are able to reduce serum cholesterol and triglyceride levels in experimentally induced hyperlipidaemic rats (Bishayee & Chatterjee 1994) and in spontaneously hypertensive rats (Preuss et al 1998), as well as in humans with type 2 diabetes (Shanmugasundaram et al 1990). These results have not yet been established by long-term studies. A recent rat experiment demonstrated reduced hyperlipidaemia and weight loss without rebound effect after the treatment was withdrawn for 3 weeks (Luo et al 2007).

OTHER USES

Gymnema has been used as a snakebite cure because it inhibits venom ATPase (Manjunatha & Veerabasappa 1982), and has also been used as a leaf paste to treat toe mycosis.

An insecticide against mosquitos may be another use due to its larvicidal properties (Gopiesh et al 2007).

In Ayurvedic medicine, gymnema is used as an antimalarial, digestive stimulant, laxative and diuretic and as a treatment for cough, fever, urinary conditions and diabetes.

DOSAGE RANGE

The typical therapeutic dose of an extract, standardised to contain 24% gymnemic acids, is 400–600 mg/day. When used to regulate blood sugar, gymnema may best be administered in divided doses with meals.

Diabetes

- Liquid extract (1:1): 25–75 mL/week or 3.6–11.0 mL/day.
- 6–60 g/day of dried leaf infusion.

Sweet craving and reducing sweet perception

- Liquid extract (1:1): 1–2 mL dropped onto the tongue and rinsed off — repeat every 2–3 hours as required.

ADVERSE REACTIONS

Theoretically, gastric irritation can occur, because of the saponin content. There are two case reports of hepatotoxicity resulting from the consumption of a weight-loss formula containing gymnema and other herbs, including *Garcinia cambogia*, willow bark, glucomannan, green tea and guarana (Stevens et al 2005). In one study, gymnema was found to have a toxic effect in mice, producing increased lipid peroxidation at doses of 26.8 mg/kg, but was safe and antiperoxidative at doses of 13.4 mg/kg (Gholap & Kar 2005). In another study it was concluded that there was no toxic effect in rats treated with gymnema at doses of more than 500 mg/kg for 52 weeks (Ogawa et al 2004).

SIGNIFICANT INTERACTIONS

Controlled studies are not available; therefore, interactions are based on evidence of activity and are largely theoretical and speculative.

Hypoglycaemic agents and insulin

Gymnema may enhance the blood glucose-lowering effects of insulin and hypoglycaemic agents, and so should be used with caution. In practice, the interaction may be useful, as a reduction in the drug dose could theoretically be achieved under professional supervision.

CONTRAINDICATIONS AND PRECAUTIONS

Blood glucose levels should be monitored closely when used in conjunction with insulin and hypoglycaemic agents.

PREGNANCY USE

There is insufficient reliable information available about the safety of gymnema in pregnancy.

PRACTICE POINTS/PATIENT COUNSELLING

- Gymnema suppresses the ability to taste sweet on the tongue.
- It may be useful as a weight-loss aid.
- Clinical studies have shown that gymnema can be used to help control blood sugar levels in diabetes.
- When used with hypoglycaemic medications, blood sugar levels need to be monitored to prevent hypoglycaemia.
- Preliminary research suggests that it may also have a role in elevated cholesterol and triglyceride levels.

PATIENTS' FAQs

What will this herb do for me?
Gymnema has the uncanny ability to reduce the tongue's perception of sweetness. It can also stabilise blood sugar levels and may be useful as a weight-loss aid.

When will it start to work?
It reduces the taste of sweetness rapidly, lasting for several hours, but effects on blood sugar develop with long-term use.

Are there any safety issues?
Diabetic patients on medication should carefully monitor their blood sugar levels when taking this herb, because it may further reduce levels.

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Hawthorn

HISTORICAL NOTE The name 'hawthorn' comes from 'hedgethorn', after its use as a living fence in much of Europe. Dioscorides and Paracelsus praised hawthorn for its heart-strengthening properties and it is also known in TCM. It has since been shown to have many different positive effects on the heart and is a popular prescription medicine in Germany for heart failure (Rigelsky & Sweet 2002).

COMMON NAME
Hawthorn

OTHER NAMES
Aubepine, bianco spino, crataegi (azarolus, flos, folium, folium cum flore [flowering top], fructus [berry], nigra, pentagyna, sinaica boiss), English hawthorn, Chinese hawthorn, fructus oxyacanthae, fructus spinae albae, hagedorn, hedgethorn, maybush, maythorn, meidorn, oneseed hawthorn, shanzha, weissdorn, whitehorn

BOTANICAL NAME/FAMILY
Crataegus laevigata, *C. cuneata*, *C. oxyacantha*, *C. monogyna*, *C. pinnatifida* (family Rosaceae [Rose])

PLANT PARTS USED
Extracts of the leaf and flower are most commonly used, although the fruit (berries) may also be used.

CHEMICAL COMPONENTS
Leaves and flowers contain about 1% flavonoids, such as rutin, quercetin, vitexin, hyperoside, 1–3% oligomeric procyanidins including catechin and epicatechin, triterpenes, sterols, polyphenols, coumarins, tannins (Blumenthal et al 2000). Although the therapeutic actions cannot be attributed to single compounds, the herb has been standardised to flavonoid content (hyperoside as marker) and procyanidins (epicatechin as marker). RP WS 1442 is a hydro-alcoholic extract of hawthorn prepared from leaves and blossoms and standardised to 18.75% oligomeric procyanidins. It has been found that bioequivalent extracts as determined by noradrenaline-induced contraction of isolated guinea pig aorta rings can be obtained using 40–70% ethanol or methanol as the extraction solvent, whereas aqueous extracts had markedly different constituents and pharmacological effects (Vierling et al 2003). In vivo absorption studies found that oral administration of hawthorn phenolic extract resulted in detectable plasma levels of epicatechin whereas no hyperoside and isoquercetin were detected, indicating poor bioavailability of these compounds (Chang et al 2005). A year later the same authors, who used in vitro and in vivo experiments, showed that all three constituents have limited permeabilities and co-occurring extract components seem to have no significant effect on their intestinal absorption (Zuo et al 2006). A recent study investigating another important constituent, vitexin-2"-*O*-rhamnoside, showed that passive diffusion dominates its absorptive transport behaviour, and that the absorption and secretion are mediated by the efflux transport system P-glycoprotein (Xu et al 2008).

MAIN ACTIONS

Cardiovascular effects
The mechanisms of action for hawthorn have been extensively studied in vitro and in vivo. There is good research evidence to support cardiovascular actions that include increasing the force of myocardial contraction (positive inotropic action), increasing coronary blood flow, reducing myocardial oxygen demand, protecting against myocardial damage, improving heart rate variability and stroke volume, as well as hypotensive and anti-arrhythmic effects (Mills & Bone 2000, Garjani et al 2000, Popping et al 1995).

Positive inotrope
One study suggested that phosphodiesterase inhibition may underlie the myocardial action of hawthorn (Schussler et al 1995), whereas a later study found that Crataegus extract's positive inotropic effect is not caused by phosphodiesterase inhibition or a beta-sympathomimetic effect (Muller et al 1999).

Anti-arrhythmic effect and negative chronotropic effect
Crataegus extract blocks repolarising potassium currents in ventricular myocytes, an effect similar to the action of class III anti-arrhythmic drugs, which might be the basis for its observed anti-arrhythmic effects (Muller et al 1999). Hawthorn therefore differs from other inotropic agents, which reduce the refractory period and increase the risk of arrhythmias (Joseph et al 1995). Additionally, hawthorn extract does not cause beta-adrenergic receptor blockade at concentrations which cause negative chronotropic effects (Long et al 2006). A recent study elucidated that the decreased chronotropic effect in rat cardiomyocytes may be mediated via muscarinic receptors (Salehi et al 2009).

Cardioprotective effect
Interestingly, hawthorn treatment modifies left ventricular remodelling and counteracts myocardial dysfunction in animal models of cardiac hypertrophy (Hwang et al 2008). Furthermore, in vitro and in vivo studies on rats report a significant cardioprotective effect during cardiac ischaemia (Al Makdessi et al 1996, 1999, Jayalakshmi & Devaraj 2004, Min et al 2005, Veveris et al 2004). For example, pretreatment with alcohol-based hawthorn extract maintained mitochondrial status, and prevented mitochondrial lipid peroxidative damage and decrease in Kreb's cycle enzymes following induced myocardial infarction in rats (Jayalakshmi et al 2006).

Coronary blood flow

Dose-dependent increases in coronary blood flow have been shown in isolated human coronary arteries and it has been suggested that this is caused by membrane hyperpolarisation of vascular smooth-muscle cells due to potassium channel activation (Siegel et al 1996). When testing hawthorn extract WS 1442 for its effect on relaxation of rat aorta and human mammalian artery, researchers discovered that the extract induces an endothelium dependent, NO-mediated vasorelaxation (Brixius et al 2006).

Much of hawthorn's cardiovascular activity is attributed to its flavonoid constituents (Nemecz 1999) and hawthorn extract is classified as a flavonoid drug in Germany. Studies using isolated guinea pig hearts suggest that the oligomeric procyanidins contribute to the vasodilating and positive inotropic effects of hawthorn (Schussler et al 1995), and ischaemia–reperfusion studies in rats suggest that these compounds are also responsible for cardioprotective effects (Chatterjee et al 1997).

It has been reported that hawthorn extracts prepared from dried leaves and those made from dried berries have similar chronotropic activities and that the extracts may contain multiple dissimilar cardioactive components, because following various chromatographic steps several fractions retained multiple cardiac activities (Long et al 2006).

Several procyanidins have shown ACE inhibition in vitro, in a reversible and non-competitive manner (Uchida et al 1987). Although the original study identifying this activity tested isolated procyanidins from another herb, they are found in relatively high concentration in hawthorn extracts (Murray 1995).

Antioxidant

It has been suggested that the part of the mechanism for hawthorn's cardiovascular protective effects may be due to protection against human LDL from oxidation or indirect protection via maintenance of alpha-tocopherol (Zhang et al 2001), as hawthorn extract has been found to possess antioxidant activity in vitro (Periera et al 2000, Rajalakshmi et al 2000) with effective inhibition of oxidative processes, efficient scavenging of O_2 and possible enhancement of glutathione biosynthesis (Ljubuncic et al 2005). Along those lines newer research shows that ethanolic hawthorn extract restores glutathione and the activity of antioxidant enzymes such as superoxide dismutase, catalase and glutathione peroxidase (Akila & Devaraj 2008).

Hawthorn's free radical scavenging capacity is considered to relate to its total phenolic proanthocyanidin and flavonoid content (Bahorun et al 1996, Rakotoarison et al 1997, Kiselova et al 2006). This is supported by a study that demonstrated that the capacity of hawthorn extracts to inhibit Cu^{2+}-induced LDL oxidation is linked to their content of total polyphenols, proanthocyanidins (global and oligomeric forms), as well as to their content of two individual phenolics: a flavonol, the dimeric procyanidin B2, and a flavonol glycoside, hyperoside (Quettier-Deleu et al 2003). The highest antioxidant activity appears to be found in the flower buds, which are high in proanthocyanidin content, and the leaves, which are high in flavonoid content (Bahorun et al 1994). Recent research has confirmed these findings, with fresh and dried fruits possessing less antioxidant activity and, amongst all other classes of phenols in hawthorn, proanthocyanidins are most clearly related to the antioxidant activity of hawthorn extracts (Froehlicher et al in press). Epicatechin was found to be more efficient as an antioxidant than hyperoside or chlorogenic acid (Bernatoniene et al 2008, Froehlicher et al in press, Sokól-Letowska et al 2007). Bernatoniene et al found that both aqueous and ethanolic hawthorn extracts have antiradical activity, but that the effect displayed by the ethanolic extract was stronger (Bernatoniene et al 2008). Moreover, the radical scavenging properties were higher for both extracts when a combination rather than individual constituents were used (Bernatoniene et al 2008, Sokól-Letowska et al 2007).

Lipid-lowering

The monomeric catechins and oligomeric procyanidins are thought to contribute to a hypocholesterolaemic effect. This may occur through a variety of mechanisms including an upregulation of hepatic LDL receptors, enhanced degradation of cholesterol to bile acids, and suppression of cholesterol biosynthesis (Rajendran et al 1996), as well as inhibition of cholesterol absorption mediated by downregulation of intestinal acyl CoA:cholesterol acyltransferase activity (Zhang et al 2002). Moreover, in mice hawthorn flavonoids increased lipoprotein lipase expression in muscular tissue and decreased it in adipose tissue (Fan et al 2006). Hawthorn extract, when fed to rats on an atherogenic diet (4% cholesterol, 1% cholic acid, 0.5% thiouracil), prevented the elevation of lipids in the serum and heart, and also significantly decreased lipid accumulation in the liver and aorta, thus reversing the rats' hyperlipidaemic conditions (Akila & Devaraj 2008).

A traditional multi-herbal Chinese formula containing hawthorn has been found to prevent experimental hypercholesterolaemia in rats, probably due to its choleretic function (Cheng et al 2004). A different multi-herbal Chinese formula was also found to protect vascular endothelial cells from excess cholesterol in vivo (Tu et al 2003).

Antiviral

The *O*-glycosidic flavonoids and the oligomeric proanthocyanidins exhibited significant inhibitory activity against herpes simplex virus type 1 in vitro (Shahat et al 2002).

Antimicrobial

Hawthorn extracts showed moderate bactericidal activity, especially against gram-positive bacteria *Micrococcus flavus*, *Bacillus subtilis* and *Lysteria monocytogenes*. Hawthorn was ineffective against *Candida albicans* (Tadic et al 2008).

Anti-inflammatory

Flavonoids from hawthorn have demonstrated anti-inflammatory and hepatoprotective activity in vitro and in vivo. It is thought that this is achieved by reducing the release of PGE_2 and NO in vitro, as

well as decreasing the serum levels of the hepatic enzyme markers, reducing the incidence of liver lesions, such as neutrophil infiltration and necrosis, and decreasing the hepatic expression of iNOS and COX-2 in vivo (Kao et al 2005).

A hydro-alcoholic extract from the flower heads of *C. oxyacantha* has also been found to inhibit thromboxane A2 biosynthesis in vitro (Nemecz 1999).

Chemopreventative effects have been postulated after the inhibition of skin tumour formation, a decrease in the incidence of tumour, inhibition of NF-kappa B and suppressed expression of COX 2 and iNOS were detected when using the polyphenol fraction of hot water extracts from dried fruits of *C. pinnatifida* (Kao et al 2007).

A dry extract of leaves and flowers of *C. laevigata* inhibited N-formyl-Met-Leu-Phe (FMLP)-induced superoxide anion generation, elastase release and chemotactic migration in human neutrophils. It also reduced FMLP-induced leukotriene B(4) production and LPS-induced generation of TNF-alpha and IL-8 (Dalli et al 2008).

In a study using 62 male rats no effect on IL-1ss, IL-6, IL-10 and leptin could be detected. However, there was a trend suggesting suppression of IL-2 plasma concentrations (Bleske et al 2007).

Hawthorn fruit has been shown to be protective in experimental models of inflammatory bowel disease in mice with restoration of body weight and colon length, increased haemoglobin count, reduced signs of inflammation, such as infiltration by polymorphonuclear leukocytes and multiple erosive lesions, along with improved survival (Fujisawa et al 2005). In a model of carrageenan-induced rat paw oedema, orally administered hawthorn extract showed dose-dependent anti-inflammatory effects. Compared to an indomethacin dose producing 50% reduction of rat paw oedema, a dose of 200 mg/kg hawthorn extract produced 72.4% of anti-inflammatory activity (Tadic et al 2008).

Radioprotective

A study using mouse bone marrow cells showed that a single intraperitoneal administration of hawthorn extract 1 hour prior to gamma radiation can significantly reduce the frequencies of micronucleated polychromatic erythrocytes and significantly increase the ratio of polychromatic erythrocyte/polychromatic erythrocyte + normochromatic erythrocyte. Such a protective effect against genotoxicity appeared to be related to the antioxidant activity of the extract (Hosseinimehr et al 2007). The significant radioprotective potential of hawthorn was also detected in vitro using human peripheral blood lymphocytes. A reduced incidence of radiation induced micronuclei, reduced levels of lipid peroxidation products and two-fold enhanced apoptosis were observed. A stepwise slow down of cell proliferation was seen as beneficial, thus enabling more time for repair (Leskovac et al 2007).

Protection against ischaemic damage

Hawthorn flavonoids have also been shown to decrease the cytotoxicity of hypoxia to human umbilical vein endothelial cells in vitro (Lan et al 2005), as well as protect against delayed cell death caused by ischaemia/reperfusion brain injury in gerbils (Zhang et al 2004). These effects have been attributed to improving energy metabolism, scavenging oxygen free radicals and inhibiting production of free radicals in ischaemic myocardium (Min et al 2005, Zhang et al 2004).

OTHER ACTIONS

Hawthorn may decrease uterine tone and motility and exert antispasmodic and analgesic effects. The high procyanidin content in the herb provides a theoretical basis for other actions such as anti-allergic and collagen-stabilising effects. Moreover, a hawthorn extract has been shown to produce dose-dependent gastroprotective activity, with the efficacy comparable to ranitidine (Tadic et al 2008).

An aqueous extract of hawthorn leaves exhibited hypoglycaemic activity in streptozotocin-diabetic rats, but not in normal rats, without affecting basal plasma insulin concentrations (Jouad et al 2003). Hawthorn has also been found to have hepatoprotective effects in rats with myocardial infarction, with protection against alterations in tissue marker enzymes of experimentally induced liver injury and a reversal of histological changes (Thirupurasundari et al 2005). A multi-herbal Chinese medicine formula containing hawthorn reversed alcohol-induced fatty liver and liver damage in rats (Kwon et al 2005).

CLINICAL USE

Congestive heart failure

There is considerable experimental and clinical evidence supporting the use of hawthorn as an effective treatment for congestive cardiac failure in patients with slight, mild limitation of activity who are comfortable at rest or with mild exertion (i.e. NYHA class II).

A meta-analysis of rigorous clinical trials of the use of hawthorn extract to treat patients with chronic heart failure (NYHA classes I–III) included eight trials involving 632 subjects. The results of the meta-analysis showed that treatment with standardised hawthorn extracts produced significant improvement in maximal workload, pressure–heart rate product, as well as symptoms such as dyspnoea and fatigue as compared with placebo (Pittler et al 2003). The hawthorn extract most commonly used in these trials was WS 1442, which is standardised to 18.8% oligomeric procyanidins. In some cases, hawthorn extract was used as an adjunct to standard therapy (such as diuretics) and the daily dose ranged from 160 mg to 1800 mg.

A review of the results of 13 clinical trials published from 1981 to 1996, involving over 839 patients, suggests that a daily dose of 900 mg hawthorn extract improves exercise tolerance, anaerobic threshold and ejection fraction, as well as subjective symptoms (Kraft 2000). Studies comparing hawthorn extract LI 132 (Crataegutt novo 450, 1 tablet twice daily) to the ACE inhibitor captopril suggests that the LI 132 extract is comparable in effectiveness to a dose of 37.5 mg captopril, but may be better tolerated (Tauchert et al 1994).

Similarly, a prospective, cohort study involving 952 patients with NYHA stage II heart failure compared the use of the WS 1442 extract of hawthorn either alone or in conjunction with conventional therapy to conventional medication. After 2 years, the hawthorn cohort was found to have similar or more pronounced improvements than the conventional medication group with reduced fatigue, stress dyspnoea and palpitations, along with marked reduction in the use of drugs such as ACE inhibitors, cardiac glycosides, diuretics and beta-blockers (Habs 2004).

In two further double-blind studies of NYHA class II patients, one using the WS 1442 extract in 40 patients (Zapfe 2001) and another using the Rob 10 standardised extract of fresh hawthorn berries in 88 patients (Rietbrock et al 2001), 3 months' treatment with hawthorn led to significantly improved exercise tolerance, reduced subjective symptoms, and was found to be safe and well tolerated. In 2003, another placebo-controlled, randomised, parallel-group, multicentre trial confirmed the efficacy and safety of a standardised extract of fresh berries of *Crataegus oxyacantha* L. and *C. monogyna* Jacq. (crataegisan) in patients with cardiac failure NYHA class II (Degenring et al 2004). This study of 143 patients (mean age 64.8 years) used a dose of 30 drops of the extract taken three times daily for 8 weeks and found a significant increase in exercise tolerance, but no difference in symptoms or blood pressure–heart rate product. Researchers suggested that dyspnoea and fatigue do not occur until a significantly higher wattage had been reached in the bicycle exercise testing and that further improvements were likely to occur if treatment time was extended.

In another RCT of patients with marked limitation of activity, who were comfortable only at rest (NYHA class III), 209 patients received standardised extract WS 1442 at doses of either 900 mg or 1800 mg or placebo in addition to pre-existing diuretic treatment. After 16 weeks, significant dose-dependent improvements in exercise capacity and clinical signs and symptoms were seen with the herbal extract, with patients on the higher dosage experiencing less adverse events such as dizziness and vertigo (Tauchert 2002).

A 2008 Cochrane review of 14 randomised, placebo-controlled, double-blind clinical trials concluded that in patients using hawthorn extract symptoms such as shortness of breath and fatigue significantly improved, exercise tolerance significantly increased, the outcome measure of maximal workload significantly improved and the pressure-heart rate product (index for cardiac oxygen consumption) beneficially decreased. No data on relevant mortality and morbidity such as cardiac events were reported, except for one trial which reported deaths (three in active, one in control) without providing further details (Pittler et al 2008).

A large, international, multicentre, randomised, double-blind, placebo-controlled study investigated the efficacy and safety of WS 1442 extract (900 mg daily) in 2681 patients with NYHA class II or III CHF and reduced left ventricular ejection fraction (LVEF ≤ 35%) over 24 months (Holubarsch et al 2008). The trend for cardiac mortality reduction was not statistically significant. However, in the subgroup with LVEF ≥ 25% WS 1442 significantly reduced sudden cardiac death by 39.7% ($P = 0.025$) in comparison to the placebo group. It seems that WS 1442 can potentially reduce the incidence of cardiac death in patients with less compromised left ventricular function (Holubarsch et al 2008).

A retrospective study, analysing the data from the HERB CHF study in which patients with mild to moderate heart failure (HF) were randomised to 900 mg WS 1442 or placebo, found that patients taking WS 1442 had an increased risk of HF progression (HF death, hospitalisation or increase in diuretics), however, it was also reported that the patients using WS 1442 had already an increased likelihood of HF progression at baseline (Zick et al 2008). In contrast to Holubarsch et al (2008), the authors of this study found that patients with LVEF ≤ 35% who were taking WS 1442 were at significantly greater risk of HF progression than patients in the placebo group (Zick et al 2008).

In an observational cohort study of 212 patients, a homeopathic hawthorn preparation was found to be non-inferior to standard treatment (ACE inhibitor/diuretics) for mild cardiac insufficiency in all parameters except blood pressure reduction (Schroder et al 2003).

As well as being shown to be effective when used alone, hawthorn is effective in reducing symptoms of congestive heart failure when used in combination with other herbs such as camphor. This was demonstrated in an open study of 319 patients (Harder & Rietbrock 1990), as well as in a double-blind study of 190 patients (Schmidt et al 2000).

Commission E supports the use of hawthorn leaf and flower to treat decreased cardiac output (NYHA class II) (Blumenthal et al 2000).

Arrhythmias, hypertension and atherosclerosis

In addition to treating congestive cardiac failure, hawthorn has traditionally been used to treat arrhythmias, hypertension and atherosclerosis, with some evidence to support these uses, although large controlled clinical studies are required (Petkov 1979).

In one double-blind RCT of 92 subjects aged 40–60 years, a hydro-alcoholic extract of Iranian hawthorn (*C. curvisepala* Lind) given three times daily was found to produce a significant decrease in both systolic and diastolic blood pressure after 3 months. Antihypertensive activity was also observed in one uncontrolled study that used hawthorn berry tincture (equivalent to 4.3 g/day of berry) (Mills & Bone 2000), whereas three randomised, double-blind, placebo-controlled clinical trials have shown that a combination of natural D-camphor and an extract from fresh hawthorn berries was effective in treating orthostatic hypotension (Georg Belz & Loew 2003, Hempel et al 2005, Kroll et al 2005). Furthermore, when this combination of natural D-camphor and an extract from fresh hawthorn berries (marketed as Korodin®) was given to hypotensive women in two

randomised, double-blind, placebo-controlled, clinical trials, the treatment led to positive and differential effects on blood pressure and cognitive performance compared to placebo within 5 min (Schandry & Duschek 2008).

One study that focused primarily on mild hypertension compared the hypotensive effect of low dose hawthorn extract (500 mg) and magnesium supplements, individually and in combination, to placebo. Walker et al (2002) found hawthorn treatment significantly reduced resting diastolic blood pressure at week 10 compared with the other groups. In addition, a trend towards a reduction in anxiety was also observed with hawthorn treatment, which is an interesting observation as sedative effects have been observed in animal models.

A recent randomised, placebo-controlled, clinical trial ($n = 79$) focused for the first time on investigating possible hypotensive effects of hawthorn extract (1200 mg daily) in patients with type 2 diabetes while taking their prescription drugs. Hypotensive drugs were used by 71% of the participants with a mean intake of 4.4 hypoglycaemic and/or hypotensive drugs. In general, fat intake met recommendations, whereas sugar intake was higher than recommended, and micronutrient intake was low. The hawthorn group showed significantly greater reduction than the placebo group in mean diastolic blood pressure, but not in systolic blood pressure (Walker et al 2006).

Hyperlipidaemia

Hawthorn fruit extract has been reported to reduce serum lipid levels, as well as to reduce lipid deposits in the liver and aortas of rats (Shanthi et al 1994) and rabbits (Zhang et al 2002) fed a hyperlipidaemic diet. In combination with other traditionally used Chinese herbs, hawthorn has been shown to also reduce serum lipid levels in both animals (He et al 1990, La Cour et al 1995) and humans (Chen et al 1995, Guan et al 1995).

Adjustment disorder

The results of a double-blind trial of 182 people suggest that hawthorn in combination with other herbs such as passionflower and valerian may be beneficial for people with adjustment disorder with anxious mood (Bourin et al 1996). Another double-blind trial of 264 people found that a combination containing *Crataegus oxyacantha* and *Eschscholtzia californica* along with magnesium was effective in treating mild-to-moderate anxiety disorder (Hanus et al 2004).

OTHER USES

As it has a high flavonoid content, hawthorn is also used to strengthen connective tissue, decrease capillary fragility, and prevent collagen destruction of joints and therefore may be beneficial in the treatment of certain connective tissue disorders (Mills & Bone 2000). Hawthorn has been traditionally used as a diuretic and to treat kidney and bladder stones. In practice, it is also used at the first signs of a herpes simplex infection, to prevent lesion formation and halt infection.

DOSAGE RANGE

- Infusion of dried herb: 0.2–2 g three times daily.
- Tincture of leaf (1:5): 3.5–17.5 mL/day.
- Fluid extract (1:2): 3–6 mL/day.
- Dry extract: 900–1200 mg/day.
- Herpes simplex outbreak: 4 mL three times daily at the first sign of infection for a maximum of 2 days.

TOXICITY

No target toxicity to 100-fold the human dose of the WS 1442 extract is defined (Schlegelmilch & Heywood 1994). This is in contrast to inotropic drugs, such as digoxin, which generally have a low therapeutic index. A recent preclinical toxicological assessment for a combination product consisting of hawthorn, passionflower and valerian showed no toxicity at high doses and over a long period of time (180 days) (Tabach et al 2009).

ADVERSE REACTIONS

A systematic review (24 clinical trials, $n = 5577$ patients) concluded that hawthorn extracts (mostly WS 1442, LI 132) were well tolerated at doses between 160 and 1800 mg daily for a duration of 3 to 24 weeks. Overall, 166 adverse events were reported, most of which were mild to moderate. Eight severe adverse effects had been reported with the LI 132 extract. The most frequent adverse effects were dizziness/vertigo ($n = 15$), gastrointestinal complaints ($n = 24$), headache ($n = 9$), migraine ($n = 8$) and palpitation ($n = 11$) (Daniele et al 2006). Similarly, a recent review of 14 clinical trials reported safe use of hawthorn with only infrequent, mild and transient adverse effects such as dizziness, cardiac and gastrointestinal complaints (Pittler et al 2008).

SIGNIFICANT INTERACTIONS

WS 1442 (900 mg daily) was safe to use in patients ($n > 2500$) receiving optimal medication for heart failure (Holubarsch et al 2008). A systematic review (24 clinical trials) on the safety of hawthorn monopreparations found no reports of drug interactions (Daniele et al 2006).

Cardiac glycosides

Hawthorn may theoretically potentiate the effects of cardiac glycosides, as both in vitro and in vivo studies indicate that it has positive inotropic activity. Furthermore, the flavonoid components of hawthorn may also affect P-glycoprotein function and cause interactions with drugs that are P-glycoprotein substrates, such as digoxin. In practice, however, a randomised crossover trial with eight healthy volunteers evaluating digoxin 0.25 mg alone for 10 days and digoxin 0.25 mg with *Crataegus* special extract WS 1442 (hawthorn leaves with flowers) 450 mg twice daily for 21 days found no significant difference to any measured pharmacokinetic parameters, suggesting that hawthorn and digoxin in these doses may be co-administered safely (Tankanow et al 2003). Caution — use under professional supervision and monitor drug requirements.

Antihypertensive drugs

Theoretically, hawthorn may potentiate blood pressure-lowering effects, thereby requiring modified drug doses. However, hawthorn extract (1200 mg daily) was safe to use in patients with type 2 diabetes ($n > 70$) while taking their prescription drugs (mean intake of 4.4 hypoglycaemic and/or hypotensive drugs) (Walker et al 2006). In general, observe patients taking this combination and monitor drug requirements — interaction would be beneficial under professional supervision.

PREGNANCY USE

Hawthorn did not have an adverse effect on embryonic development in vitro and in vivo (Yao et al 2008). However, in vivo and in vitro evidence of uterine activity has been reported, therefore this herb should not be used in pregnancy until safety is established (Newell et al 1996).

PRACTICE POINTS/PATIENT COUNSELLING

- Hawthorn has positive inotropic action, increases coronary blood flow, reduces myocardial oxygen demand, protects against myocardial damage, improves heart rate variability, as well as having hypotensive and anti-arrhythmic effects.
- Although considered relatively effective, heart disease can be a very serious medical condition with a rapidly changing course and should not be treated without close medical supervision. In particular, chest pain and shortness of breath are extremely serious symptoms that require immediate medical attention.
- It may take 2–6 weeks' treatment to notice a benefit of treatment with hawthorn, and heart rate and blood pressure should be monitored.
- Hawthorn also exhibits antioxidant, anti-inflammatory, antiviral and lipid-lowering activity.
- Great care should be exercised if hawthorn is to be combined with other drugs that affect the heart.

PATIENTS' FAQs

What will this herb do for me?

Hawthorn appears to be useful in treating a variety of heart conditions such as high blood pressure, hyperlipidaemia and heart failure.

When will it start to work?

Studies suggest it will start to have effects in 2–6 weeks.

Are there any safety issues?

Heart conditions are potentially serious, therefore professional supervision is required.

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Honey

HISTORICAL NOTE Honey has been used since ancient times as a healing agent for wounds and a treatment for gastric complaints. In ancient Greece, Hippocrates recommended honey and vinegar for pain and honey combinations for fever. It is also recommended by the Bible and the Koran as a medicinal agent. Over the past few decades, scientific research has confirmed its role as a successful wound treatment. It is also known as *honig* and *miel blanc*.

CHEMICAL COMPONENTS

Caffeic acids, benzoic acid and its esters, phenolic acid and its esters, flavonoids, beeswax, inhibin, glucose oxidase and catalase, although other as yet unidentified constituents also exist (Aysan et al 2002).

The composition of a particular honey greatly depends on the composition of the nectar it originated from, and therefore the plant species involved in its production.

MAIN ACTIONS

Antibacterial

The type of plant species involved in honey production is significant, as some confer greater antibacterial properties than others. Currently, evidence suggests that honey produced from the tea trees *Leptospermum scoparium* (New Zealand manuka) and *Lipolygalifolium* (Australian jelly bush) are the most effective, but batch testing is still required to verify the antibacterial activity of commercially produced preparations. However, other honeys, not specifically promoted for their antibacterial qualities, may still have antibacterial activity (Lusby et al 2005).

Several mechanisms of action account for the antibacterial effect of honey.

Hydrogen peroxide content

Hydrogen peroxide has antiseptic properties and is naturally produced in honey. The relative levels of two enzymes, glucose oxidase and catalase, within honey influence the amount of hydrogen peroxide produced. Additionally, diluting full-density honey encourages greater hydrogen peroxide and gluconic acid production from glucose (Aysan et al 2002). Differences in antimicrobial activity among honeys from various floral sources may, in part, be a reflection of these natural variations.

High osmolarity

Honey has a high sugar and low water content, with sugar concentration reaching up to 80% in some seasons. Its high osmolarity is considered important because sugar molecules bind to the existing water molecules, thereby reducing the amount of water available to bacteria.

Low pH

Honey is an acidic substance and therefore unfavourable to the growth of certain bacteria. In vitro testing shows that *Leptospermum* honey can inhibit the growth of several important bacterial pathogens, including *Escherichia coli*, *Salmonella typhimurium*, *Shigella sonnei*, *Listeria monocytogenes*, *Staphylococcus aureus*, *Bacillus cereus* and *Streptococcus mutans* (Steinberg et al 1996, Taormina et al 2001).

In a recent open-label, non-randomised prospective study, applying a manuka honey dressing to non-healing wounds was associated with a statistically significant decrease in wound pH and size. A reduction in pH of 0.1 was associated with an 8.1% reduction in wound size (Gethin et al 2008).

The antibacterial action of honey may be enhanced when combined with a synergistic compound. The antibacterial and antifungal activities of honey were increased by the addition of starch to the medium (Boukraa & Bouchegrane 2007, Boukraa & Amara 2008). When Royal Jelly was combined with four different samples of honey, the minimum inhibitory concentration (MIC) against *Staphylococcus aureus* was lowered by 50% (Boukraa et al 2008).

Honey has also been tested for efficacy against a range of drug-resistant bacteria, with positive results (Cooper et al 2002). Eighteen strains of methicillin-resistant *Staphylococcus aureus* and 27 strains of vancomycin-sensitive and -resistant enterococci, isolated from infected wounds and hospital surfaces, were sensitive to concentrations below 10% w/v of manuka honey and pasture honey. Artificial honey was also effective, but concentrations three times greater were required to produce similar results. In a study using a 10%–40% v/v medical-grade honey (Bfactory) applied to the skin of healthy volunteers colonised with antibiotic-susceptible and -resistant isolates of *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Enterococcus faecium*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Enterobacter cloacae* and *Klebsiella oxytoca*, bacterial levels were reduced 100-fold by day 2, and the number of positive skin cultures was reduced by 76% (Kwakman et al 2008).

Honey is effective (in vitro) against community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA), which typically infects skin and soft tissues in healthy individuals. Culture counts of 10^6 colony-forming units were reduced to a non-detectable amount in 24 h in the four honey samples tested whilst levels in the control group (no honey) remained unchanged (Maeda et al 2008).

Phenolic compound

The antioxidant activity of honey has been associated with the levels of phenolic compounds found in a range of floral honeys, with antioxidant activity varying between 43.0% and 95.7%. The responsible compounds suggested include p-coumaric acid, kaempferol, chrysin and apigenin (Baltrusaityte et al 2007). The variation in the concentration of the phenolic compounds among different floral honeys is further confirmed through another study, which found that the concentration of millefiori honey is the highest in polyphenols, flavonoids and has a corresponding high antioxidant activity, when compared with *Acacia* honey (Blasa et al 2006).

Antifungal

Honey has an antifungal action against three species of *Candida* in vitro (Irish et al 2006). Isolates of *C. albicans*, *C. glabrata* and *C. dubliniensis* were tested against four samples of honey; Jarrah honey with hydrogen peroxide activity, Medihoney Antibacterial Honey Barrier, a proprietary blend of *Leptospermum* and hydrogen peroxide honeys, Comvita Wound Care, a pure *Leptospermum* honey, and an artificial honey. The natural honeys had a significantly greater antifungal effect compared to the artificial honey against *C. albicans* and *C. glabrata*, but only the Jarrah honey was effective against *C. dubliniensis*.

Deodorises wounds

Bacteria use the glucose found in honey in preference to amino acids, thereby producing lactic acid instead of malodorous products (Molan 2001).

Debriding

The topical application of honey to a wound tends to lift debris to the surface, allowing for easier cleaning, which may be related to its high osmolarity. Honey does not adhere to the surface, allowing for easier and less painful wound dressing changes (Subrahmanyam 1998).

Enhances wound healing

Clinical evidence suggests that the application of honey hastens granulation and epithelialisation of necrotic tissue by various mechanisms. It appears to stimulate the growth of new blood capillaries and cytokine production, thereby stimulating tissue regeneration. The high viscosity of honey and its hygroscopic character allow it to form a physical barrier, creating a moist environment and a reduction in local oedema (Aysan et al 2002). Clinically, it appears that epithelialisation is accelerated between days 6 and 9 (Subrahmanyam 1998), and that honey is more beneficial than Edinburgh University solution of lime (EUSOL) as a wound-dressing agent (Okeniyi et al 2005).

Antioxidant

The phenolic compounds found in honey, namely the flavonoids, render it a good source of antioxidants (Al-Mamary et al 2002, Schramm et al 2003). In vitro tests have confirmed a significant link between absorbance and antioxidant power, with darker, more opaque honeys having stronger antioxidant power than lighter, clearer honeys (Taormina et al 2001). More specifically, manuka honey has been identified to be a specific scavenger of superoxide anions (Inoue et al 2005). A study examining different samples of honey for their ability to reduce reactive oxygen species (ROS) in vitro found significant variation in activity, with buckwheat honey most effective. This is possibly due to its high concentration of phenolic compounds, which have known antioxidant activity. Considering the fact that hydroxyl radicals

and hypochlorite anions formed in the wound site impair wound healing, this honey should have superior wound healing properties (van den Berg et al 2008).

Immunomodulation

An animal study has shown that both immunocompetent and immunodeficient mice had increased humoral immunity following administration with honey (Karmakar et al 2004).

OTHER ACTIONS

An in vitro study showed that honey prevented binding of *Salmonella interiditis* to intestinal epithelial cells (Alanqdy et al 2005) at dilutions of up to 1:8.

Preliminary studies suggest that honey may have an impact on reducing the intoxicating effects of alcohol; however, that research was of questionable quality, and a better standard of research is required to validate this effect (Onyesom 2004, 2005).

Honey may also have an antimutagenic activity against a common food carcinogen and mutagen, Trp-p-1 (Wang et al 2002).

CLINICAL USE

Honey is mainly used topically for wound healing or dermatological conditions; however, it is now being used in mouthwashes, oral syrups and ocular preparations.

Burns

Honey-dressed wounds had a more rapid reduction in local inflammation, better infection control and more rapid healing than for standard treatment with silver sulfadiazine (SSD) in a randomised clinical trial (Subrahmanyam 1998). Of the 25 patients with wounds, 84% treated with honey achieved satisfactory epithelialisation by day 7 and 100% by day 21 compared with 72% and 84%, respectively with SSD. Histological evidence confirmed honey's superiority, with 80% of wounds showing significant reparative activity and decreased inflammation by day 7 compared with 52% with SSD.

Wound healing

Honey applications have been used to treat various types of wounds, such as leg ulcers and bed sores. Honey has also been used to enhance postoperative wound healing and partial-thickness wounds such as split-thickness skin graft donor sites. Numerous studies have evaluated the efficacy of honey for these indications and found that effects are better than placebo. Whether topical honey is better than current treatments is difficult to determine, as studies have produced mixed results, mostly indicating similar effectiveness. Overall, evidence is encouraging; however, there is still a lack of double-blind studies, despite substantial interest in honey as a wound-healing agent. One reason for this may be the difficulty in selecting a suitable placebo topical application (Molan 2006).

In one study, 59 patients with wounds or ulcers not responding to conventional treatment were treated with topical unprocessed honey. Of these, 58 cases were reported as showing remarkable recovery, with all sterile wounds remaining sterile until healed and infected wounds becoming sterile within 1 week. The one case that did not respond involved a malignant ulcer. Clinically, honey promoted rapid debridement of wounds, epithelialisation and reduced oedema surrounding the ulcers (Efem 1988). Vardi et al (1998) found that 5–10 mL of unprocessed honey applied twice daily to infants not responding to at least 2 weeks of conventional treatment was able to produce a marked clinical improvement within 5 days and complete wound closure after 21 days.

A case series of eight consecutive cases examined the efficacy of honey on non-healing lower limb ulcers. After 4 weeks of using a manuka honey dressing, ulcers decreased in size by a mean of 55% and were no longer malodorous. Patients whose ulcers had an arterial component reported the least benefit and also a stinging sensation following application (Gethin & Cowman 2005). One randomised study involving 40 patients with open or infected wounds compared honey to sugar dressings (Mphande et al 2007). In the honey group, 55% of patients had positive wound cultures at the start of treatment and 23% at one week, compared with 52% and 39% respectively in the sugar group. Additionally, the median rate of healing in the first two weeks of treatment was 3.8cm^2/week for the honey group and 2.2cm^2/week for the sugar group and after three weeks of treatment 86% of patients treated with honey had no pain during dressing changes, compared with 72% treated with sugar.

Emsen (2007) used medical honey for the fixation of the split-thickness skin grafts in 11 patients. Oedema and the amount of wound exudate were reduced, and no complications such as graft loss or infection were reported either on fifth day of grafting or at the end of the follow-up period (average 17 months). A honey-medicated dressing was tested for ease of use and efficacy in a study involving 60 patients with chronic, complicated surgical or acute traumatic wounds (Ahmed et al 2003). In 59 patients, the preparation was considered easy to use and helpful in cleaning wounds.

Several studies have compared honey dressings to currently used treatments, finding it is as effective but not necessarily more effective.

A recent open-labelled, randomised controlled trial involving 368 patients with venous ulcers found that honey dressings did not significantly decrease the time needed to heal compared to those treated with usual care (a range of dressings). After 12 weeks, 55.6% of ulcers healed in the honey-treated group and 49.7% in the usual care group. There were no significant differences found in the other parameters, including mean time to healing (63.5 days and 65.3 days in the honey and usual care groups, respectively), reduction in ulcer size, incidence of infections or quality of life between the groups (Jull et al 2008). There were also more adverse events reported in the honey-treated group, with 25% of participants reporting one or more episodes of discomfort.

A non-randomised, prospective, open study compared the effects of honey-impregnated gauze,

paraffin gauze, hydrocolloid dressings and saline-soaked gauzes in 88 patients who underwent skin grafting (Misirlioglu et al 2003). Honey gauzes produced a faster epithelialisation and reduced the sensation of pain compared with paraffin and saline-soaked gauzes. This effect was the same as that observed for hydrocolloid dressings.

The effect of honey on wound healing following toenail surgery was not found to be statistically different from the paraffin-impregnated tulle gras in a double-blind, randomised controlled trial (McIntosh & Thomson 2006). Mean healing times were 40.30 and 39.98 days for the honey group and the paraffin tulle gras group, respectively. Whilst partial avulsion wounds healed statistically and significantly faster with paraffin tulle gras, no significant difference was found in time to total avulsion compared to the honey group.

A RCT of 101 haemodialysis patients compared thrice-weekly application of Medihoney with mupirocin for the healing of catheter exit sites. This study found the honey to be safe, effective and more affordable than mupirocin for this group (Johnson et al 2005).

Fournier's gangrene

In 1996, the effects of topical unprocessed honey together with traditional treatment in a rare condition known as Fournier's gangrene (FG) were investigated (Hejase et al 1996). FG is an extensive fulminant infection of the genitals, perineum or the abdominal wall and is generally regarded as a difficult-to-manage infectious disease. The major gross pathological findings are oedema and necrosis of the subcutaneous tissues when the male genitalia are involved, necessitating aggressive treatment.

In this study, 38 patients admitted with the diagnosis of FG were treated with broad-spectrum triple antimicrobial therapy, broad debridement, exhaustive cleaning and application of unprocessed honey dressings daily for 2 weeks. Rapid changes to wound healing rate occurred after 10 days' honey use — advancing necrosis ceased, wounds became sterile, odour was reduced and fluid was absorbed from wounds. Honey also enhanced the growth and multiplication of epithelial cells from the wound edges and reduced the need for scrotal plastic surgery. As a result of the impressive results obtained, these researchers highly recommend honey dressings in gangrenous wounds, suggesting that it significantly improved patient outcomes.

OTHER USES

Allergic rhinoconjunctivitis

Honey does not reduce symptoms of allergic rhinoconjunctivitis, according to results from a randomised study of 36 volunteers (Rajan et al 2002). The study compared the effects of unpasteurised and unfiltered honey with filtered and pasteurised honey and corn syrup with synthetic honey flavouring and found that an oral dose of 1 tablespoon daily of either honey produced the same results as placebo.

Helicobacter pylori infection

Honey inhibits *H. pylori* in test tube studies (Ali et al 1991, Osato et al 1999), although no controlled studies are available to clarify its effectiveness in humans.

Periodontal disease

In vitro tests show that honey can inhibit the growth of oral bacteria (Steinberg et al 1996). As a follow-up investigation, 10 volunteers were asked to swish 5 mL of honey around their mouths for 4 minutes and then swallow. At 10 minutes after honey use, oral bacterial counts were significantly decreased. A pilot study has also shown that manuka honey has potential in the treatment of gingivitis and periodontal disease (English et al 2004). Thirty subjects were given either a chewable 'honey leather' or a sugarless chewing gum to chew for 10 minutes after each meal for 3 weeks. The honey group had a statistically significant reduction in mean dental plaque scores and gingivitis (assessed by percentage of bleeding sites), with no significant changes in the control group (English et al 2004).

Eczema

Topically applied honey is sometimes used to enhance skin healing and prevent infection in eczema. Although controlled trials are not available, the clinical evidence generally supporting efficacy in wound healing provides a theoretical basis for its use in this condition.

Anal fissures and haemorrhoids

A prospective pilot study examined the use of a topical preparation containing a mixture of honey, olive oil and beeswax in a ratio of 1:1:1(v/v/v) on anal fissure or haemorrhoids. Treatment for up to 4 weeks significantly reduced the bleeding and itching in patients with haemorrhoids and pain, bleeding and itching in patients with anal fissures (Al-Waili et al 2006).

Colon cancer

Preliminary animal studies on experimentally induced colon cancer show the potential for reduced disease development (Duleva & Bajkova 2005), but further study is necessary to validate this for clinical use.

Dysbiosis

Honey may assist in inhibiting the growth of the pathogenic bacteria *Clostridium perfringens* and *Eubacterium aerofaciens*, while not affecting, or possibly promoting, the growth of beneficial *Bifidobacterium* spp. (*B. longum*, *B. adolescentis*, *B. breve*, *B. bifidum* and *B. infantis*) (Shin & Ustunol 2005).

Coughs

In a randomised, partially double-blinded clinical trial involving 105 children, a single dose of buckwheat honey, given 30 minutes before bed, significantly reduced cough severity (47.3% versus 24.7%) and overall symptom score reduction (53.7% versus 33.4%) compared to no treatment (Warren and Cooper 2008). Similarly, Paul et al (2007)

found that a single nighttime dose of buckwheat honey given to children with an upper respiratory infection resulted in greatest symptom improvement in nocturnal cough and sleeping difficulties compared to honey-flavoured dextromethorphan treatment or no treatment.

Pain following tonsillectomy

In a prospective, randomised, placebo-controlled preliminary study involving 60 patients, 5 mL honey combined with paracetamol and antibiotics was found to be more effective in reducing postoperative pain following tonsillectomy than treatment with paracetamol and antibiotics only. The honey combination treatment group also demonstrated increased tonsillary fossa epithelialisation (Ozlugedik et al 2006).

Tear deficiency and meibomian gland disease

Topical application of honey (three times daily) was found to significantly reduce the total ocular bacterial colony-forming units (CFUs) of dry eye subjects caused by tear deficiency and/or meibomian gland disease. After 3 months, antibacterial effect was such that there was no significant difference in the CFUs of the patient groups and the non-dry eye (control) group (Albietz & Lenton 2006).

Radiotherapy and chemotherapy side effects

In a prospective, controlled, randomised study, 21 adult females who had radiotherapy to the breast or thoracic wall resulting in grade 3 skin toxicities greater than 15 mm in diameter were treated daily with either a honey or a paraffin gauze dressing. The honey-treated group reported less pain, itching or irritation as measured through daily visual analogue scale (VAS) (Moolenaar et al 2006)

Two studies examined the prophylactic effect of honey against oral mucositis, which is induced as a consequence from treatment for head or neck cancer. In a single-blind, randomised clinical trial of 40 patients, the honey treatment group swished 20 mL of honey around in their mouth and swallowed gradually 15 minutes before radiation therapy, and again 15 minutes and 6 hours after, whilst the control group rinsed with 20 mL of saline before and after radiation. The level of mucositis measured by the Oral Mucositis Assessing Scale (OMAS) was significantly lower in the honey-treated group compared to the control group (Motallebnejad et al 2008). In the second randomised controlled trial of 40 patients receiving chemotherapy and radiation (involving the oral and/or oropharyngeal mucosa), the treatment group who used a topical application of pure honey had reduced levels of mucositis and less *Candida* or bacterial colonisation compared to the control group (Rashad et al 2008)

Honey may help to reduce the extent of neutropenia experienced as a side effect of chemotherapy and thereby reduce the amount of colony-stimulating factors (CSFs) required. Thirty cancer patients who had undergone chemotherapy and developed grade 4 neutropenia requiring treated with CSFs repeated this schedule of chemotherapy combined with 5 days of treatment with Life-Mel honey. The addition of the honey treatment resulted in improvement in all cell lines with fewer cases of neutropenia (40% of patients did not require treatment with CSFs), 64% of patients retaining haemoglobin levels above 11 g/dL and only 10% of patients developing thrombocytopenia. No side effects were reported with honey treatment (Zidan et al 2006).

DOSAGE RANGE

Honey is applied topically (see 'Tips on how best to use honey in practice' below).

TOXICITY

Not applicable — mostly used externally.

A rare type of food poisoning caused by the presence of grayanotoxin has been reported, particularly in the Black Sea region of Turkey. Described as 'mad honey', the dose-dependent effects include mild symptoms such as hypersalivation, vomiting, dizziness and weakness, whilst severe intoxication can lead to potentially serious cardiac complications. No fatal cases have been reported (Koca & Koca 2007).

ADVERSE REACTIONS

A mild transient stinging may occur when applied to open wounds. If this is too uncomfortable, honey can be washed away with warm water.

Allergic reactions have also been reported, but these are considered rare.

SIGNIFICANT INTERACTIONS

None known.

Oral intake may induce CYP3A4 enzyme activity, according to a small clinical study (Tushar et al 2007).

CONTRAINDICATIONS AND PRECAUTIONS

Diabetics

Honey contains a large concentration of glucose. If applied to large open wounds, it may theoretically elevate blood sugar levels — monitor blood sugar levels.

PREGNANCY USE

Safety has not been scientifically established, but historical use suggests that it is safe.

PATIENTS' FAQs

What will honey do for me?

If you apply a honey preparation that has tested positive for antibacterial activity, it will enhance wound healing, reduce pain and inflammation, and reduce the risk of wound infection.

When will it start to work?

Studies have found that by the seventh day of use, most wounds show considerable improvement and healing.

Are there any safety issues?

Using sterile honey preparations is recommended.

PRACTICE POINTS/PATIENT COUNSELLING

- Topical application of honey has been used to enhance wound healing and infection control.
- Honey has a deodorising and debriding effect on wounds, accelerates epithelialisation and reduces inflammation and pain.
- Effects are generally seen within 7 days of use.
- Not all honeys have significant antibacterial properties; however, research has identified the New Zealand *Leptospermum* (manuka honey) and Australian jelly bush honey as having potent activity.
- The honey to be used as a topical wound-healing agent or dermatological treatment should ideally be sterile and tested for clinical activity.

TIPS ON HOW BEST TO USE HONEY IN PRACTICE*

- Ensure that there is an even coverage of the wound surface.
- Larger cavities may be filled by pouring in slightly warmed honey.
- Spreading honey on a dressing pad or gauze rather than on the wound directly will be more comfortable for the patient.
- The amount of honey needed depends on the amount of fluid leaking from the wound — if honey becomes diluted, it will be less effective; typically, 20 mL of honey is used on a 10 × 10 cm dressing.
- Cover with absorbent secondary dressings to prevent honey oozing out from the dressing. Change the dressings more frequently if the honey is being diluted — otherwise change every day or two.

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Hops

HISTORICAL NOTE Although hops is most famous for producing the bitter flavour in beer, this plant has been used since ancient times to treat digestive complaints and for its slight narcotic and sedative actions. Native Americans used it as a hypnotic. It is related botanically, though not pharmacologically, to cannabis. The climbing nature of the herb influenced its common name, as this is derived from the Anglo-Saxon *hoppan*, which means 'to climb'.

COMMON NAME
Hops

OTHER NAMES
Common hops, European hops, hop strobile, hopfen, houblon, humulus, lupulus, lupulin

BOTANICAL NAME/FAMILY
Humulus lupulus (family Cannabaceae)

PLANT PART USED
Dried strobiles

CHEMICAL COMPONENTS
Resinous bitter principles (mostly alpha-bitter and beta-bitter acids) and their oxidative degradation products, polyphenolic condensed tannins, volatile oil, polysaccharides, mainly monoterpenes and sesquiterpenes, flavonoids (xanthohumol, isoxanthohumol, kaempferol, quercetin and rutin), phenolic acids and amino acids (Blumenthal et al 2000). The volatile oil and bitter acids are the most significant components of hops, the latter providing its valuable quality in the brewing of beer. The prenylated flavonoids, particularly xanthohumol, have oestrogenic activity.

MAIN ACTIONS
Traditionally, hops is viewed as a bitter tonic with antispasmodic, relaxant and sedative actions.

Sedative
A long history of use within well-established systems of traditional medicine, together with scientific testing, have suggested that hops has significant sedative activity (Blumenthal et al 2000), probably through activation of melatonin receptors. A recent in vivo study found that both the extract of hops and a fraction containing alpha-bitter acids had significant sedative properties in mice (Zanoli et al 2005). Both extracts were also found to have an antidepressant action. The sedative activity is still under investigation in order to recognise the active principles responsible for the neuropharmacological effects observed in laboratory animals, and their mechanism of action.

Oestrogenic effects
In 1953, two German scientists followed up on a folk legend that women regularly began to menstruate 2 days after beginning to pick hops. Since then, there has been much research on the oestrogenic effects of hops. Hops showed significant competitive binding to alpha- and beta-oestrogen receptors and upregulation of progesterone receptors in vitro (Liu et al 2001). The oestrogenic activity is due to the constituent 8-prenylnaringenin (Milligan et al 1999, 2000), which is converted by intestinal microflora from isoxanthohumol (Possemiers et al 2005), and mimics the action of 17b-oestradiol,

albeit with a 17-fold lesser potency in alpha-receptor sites (in the breast, liver, CNS and uterus), and a 20,000-fold lesser potency in the beta-receptor sites (mainly in the intestine, prostate, ovaries, testes and urogenital tract). A small, randomised, double-blind, placebo-controlled study using standardised doses of 8-prenylnaringenin demonstrated systemic endocrine effects, including a decrease in LH serum concentrations, in postmenopausal women. In vitro studies also show that hop extracts exert oestrogen-like activities on bone metabolism, although later in vivo studies on rats contradict this finding (Figard et al 2007)

Moderate beer consumption can provide enough 8-prenylnaringenin to ensure some biological activity in humans, with unknown consequences to health (Possemiers et al 2006).

Possible chemopreventative effects

Angiogenesis is necessary for solid tumour growth and dissemination. In addition to angiogenesis, it has become increasingly clear that inflammation is a key component in cancer insurgence that can promote tumour angiogenesis. The hops-derived chalcone, xanthohumol, prevents angiogenesis in vivo and induces detoxification enzymes, in particular quinone reductase, which may contribute to its chemoprotective effects (Dietz et al 2005).

Xanthohumol is a very promising, potential protective agent against genotoxicity of foodborne carcinogens and has been shown to inhibit the growth of the highly angiogenic Kaposi's sarcoma tumour cells in vivo. It also demonstrates antitumour activity on B-chronic lymphocytic leukaemia cells in vitro. The prenylflavonoids are able to modulate aromatase activity, thus decreasing oestrogen synthesis, and it is hypothesised that this may have relevance for the prevention and treatment of oestrogen-dependent disorders such as breast cancer.

Antimicrobial

Hops extract and hops oil have activity against the gram-positive bacteria (*Bacillus subtilis* and *Staphylococcus aureus*) and the fungus *Trichophyton mentagrophytes* var. *interdigitale*, but almost no activity against the gram-negative bacterium *Escherichia coli* and the yeast *Candida albicans* (Langezaal et al 1992). Lupulone, in particular, has been found to have some action against gram-positive bacteria, and certain gram-negative bacteria but not against others such as *E. coli*. A review of the antimicrobial properties concluded that hops was also effective against the parasite *Plasmodium falciparum* and a range of viruses, including HSV types 1 and 2, cytomegalovirus and HIV (Gerhauser 2005). The mechanism of anti-HIV activity is not fully understood, but it is thought that the flavonoid, xanthohumol, may inhibit transcription (Wang et al 2004).

OTHER ACTIONS

Cytochrome P450 induction

Colupulone, a beta-bitter acid, was reported to induce the cytochrome P450 system and increase mRNA levels of cytochrome 2B and 3A in rats (Shipp et al 1994). Another study found that the flavonoids from hops inhibit the cytochrome P450 system in humans, in particular, cytochromes 1A1, 1B1, 1A2, but not 2E1 or 3A4 (Henderson et al 2000). A recent review concluded that hops inhibits phase 1 detoxification and enhances phase 2 by inducing quinone reductase (Gerhauser et al 2002, Stevens & Page 2004). The clinical significance of these findings is unknown.

Anti-inflammatory

In clinical trials, hops has demonstrable anti-inflammatory action. A double-blind, randomised ex vivo study comparing hops extracts with ibuprofen, demonstrates equivalence in cyclo-pxygenase (COX)-2 inhibitory action but with significant COX-1 sparing activity relative to ibuprofen. Thus hops has demonstrable anti-inflammatory action without the risk of gastrointestinal side effects found with other COX enzyme inhibitors, such as ibuprofen. The chalcones from hops, including xanthohumol, significantly reduced NO by suppressing iNOS in mouse macrophage cells (Zhao et al 2003, 2005). Xanthohumol has also been reported to inhibit the production of prostaglandin E2 (PGE2). Animal studies suggest that hops could be a useful agent for intervention strategies targeting inflammatory disorders and/or inflammatory pain in arthritis (Hougee et al 2006) but with low potential for gastrointestinal and cardiovascular toxicity. In fact, mouse studies indicate that hops extract may be useful for the prevention of gastric ulcer and inflammation, as it inhibits one of the important virulence factors responsible for *H. pylori*-induced gastritis and ulceration.

Anti-allergy

Hop extracts inhibit histamine release from rat mast cells and may be effective in the relief of symptoms of allergic rhinitis or in preventing and alleviating atopic dermatitis-like skin disease.

Clinical use

In practice, the herb is prescribed in combination with other herbal medicines, such as valerian and passionflower. As is representative of clinical practice, most studies have investigated the effects of hops in combination with other herbs.

Restlessness and anxiety

Based on the herb's sedative activity, it is likely to have some effect in the treatment of restlessness and anxiety, but careful dosing would be required to avoid sedation. This indication has been approved by Commission E and European Scientific Co-Operative on Phytotherapy (ESCOP) (Blumenthal 1998).

Sleep disturbances

Hops has been used as a bath additive for sleep disturbances. A randomised, double-blind study involving 40 patients found that taking three hops baths (4 g hops in a concentrated extract) on successive days significantly improved both objective and subjective sleep quality (Bone 1996).

Commission E and ESCOP support the use of hops for sleep disturbances, such as difficulty falling asleep and insomnia (Blumenthal et al 2000).

Studies on mice confirm that hops has a central sedating effect that can be attributed to the bitter acids and hop oil. Although there have been no human in vivo studies to support oral doses of hops as a stand-alone sedative agent, several studies have demonstrated that formulas combining hops with other sedative herbs are effective for insomnia.

A number of randomised, double-blind studies have investigated the effects of an oral preparation of hops and valerian in sleep disorders. One study observed equivalent efficacy and tolerability of a hops–valerian preparation comparable to benzodiazepine treatment, with withdrawal symptoms only reported for benzodiazepine use (Schmitz & Jackel 1998). Improvement in subjective perceptions of sleep quality was confirmed in another study, which also reported that a hops–valerian combination was well tolerated compared with flunitrazepam (Gerhard et al 1996). A pilot study (Fussel et al 2000) tested a preparation containing a fixed combination of valerian extract (500 mg) and hops extract (120 mg), known as Ze 91019, in 30 subjects with mild-to-moderate, non-organic insomnia. The treatment was used at bedtime and found to reduce sleep latency and wake time as diagnosed by polysomnographic examination. This was followed up by a randomised, double-blind, placebo-controlled, prospective clinical study which proved that the same fixed extract combination was significantly superior to the placebo in reducing the sleep latency, whilst the single valerian extract failed to be superior to the placebo. The result underlined the usefulness of hops extract for patients suffering from insomnia. In another multicentre, randomised, placebo-controlled, parallel-group study, the valerian–hops combination showed only a modest hypnotic effect relative to placebo. The same was true of the control medication, diphenhydramine. A further double-blind, randomised, placebo-controlled sleep-electroecephalogram (EEG) study showed, however, that both sleep quality and quantity significantly improved with a single dose of tincture combining valerian and hops. These findings are confusing overall, and perhaps reflect the difficulty in assessing which specific herbal treatment may be most useful in treating. A valerian–hops combination may be helpful in some situations.

Menopause

A review of the scientific literature on complementary and alternative therapies for menopausal symptoms (1966–2006) suggests that as a source of phyto-oestrogens, hops may help to alleviate menopausal symptoms and has potential for the prevention of osteoporosis and cardiovascular diseases.

A randomised, double-blind, placebo-controlled trial of a standardised extract of hops (100 μg and 250 μg 8-prenylnaringenin) demonstrated a significant reduction in menopausal discomfort, in particular hot flushes, after 12 weeks of treatment in 67 women (Heyerick et al 2005). Interestingly, no dose–response relationship could be made, as the lower standardised dose was shown to be more effective.

An open, non-controlled clinical trial in 100 postmenopausal women was performed over 12 weeks to investigate the effects of vaginal application of a gel containing phyto-oestrogens from hops extract, hyaluronic acid, liposomes and vitamin E, with the aim of testing its safety and efficacy in postmenopausal women with urogenital atrophy. The results showed a statistically significant reduction in the vaginal dryness, without any adverse effects.

Indigestion

Due to the herb's bitter nature, it is used to stimulate digestion and in the treatment of common digestive complaints such as dyspepsia and indigestion. Animal studies on rats show that hops increases gastric juice volume.

OTHER USES

Traditionally, hops is also used to treat neuralgia, depression and pain and to wean patients off pharmaceutical sedative medicines. Topically it is used to treat leg ulcers and oedema.

Cancer prevention

Xanthohumol and its oxidation product may be potentially useful as a chemopreventive agent during prostate hyperplasia and prostate carcinogenesis, acting via induction of apoptosis and down-regulation of NF[kappa]B activation in BPH-1 cells. Clinical studies are required to confirm significance.

Diabetes

Isohumulones, the bitter compounds in hops, have been shown to improve insulin resistance and hyperlipidaemia in several animal models and may prevent the progression of renal injury caused by hypertension via an antioxidative effect. Clinical studies are required to confirm significance.

Periodontitis

In vitro studies suggest that the hop-derived polyphenols are potent inhibitors of prostaglandin E2 production by gingival epithelial cells stimulated with periodontal pathogen and may be useful for the prevention and treatment of periodontitis. The clinical significance of this finding is unknown and remains to be tested.

DOSAGE RANGE

- Infusion or decoction: 0.5 g in 150 mL water.
- Fluid extract (1:1) (g/mL): 0.5 mL/day; 0.5–1 mL three times daily.
- Tincture (1:5) (g/mL): 1–2.5 mL/day.
- Also used as a bath additive (4 g hops in a concentrated extract) and in pillows.

TOXICITY

Not known

ADVERSE REACTIONS

Drowsiness is theoretically possible at excessive doses. Contact with the herb or oil has resulted in reports of systemic urticaria, allergic dermatitis,

respiratory allergy and anaphylaxis (Pradalier et al 2002).

SIGNIFICANT INTERACTIONS

Interactions reported here are theoretical and yet to be tested clinically for significance.

Pharmaceutical sedatives

Additive effects are theoretically possible — observe the patient (this interaction may be beneficial).

Drugs metabolised chiefly with CYP2B or CYP3A

Altered drug effect — cytochrome (CYP) induction and inhibition have been demonstrated. However, it is unknown whether these effects are clinically significant — observe the patient for signs of altered drug effectiveness.

Anti-oestrogenic drugs

Hops may alter the efficacy of these medicines; use with caution in patients taking antioestrogenic drugs.

CONTRAINDICATIONS AND PRECAUTIONS

According to one source, hops should be used with caution in depression (Ernst 2001). Due to the herb's oestrogenic activity, disruption to the menstrual cycle is considered possible. Use is contraindicated in patients with oestrogen-dependent tumours.

PREGNANCY USE

Caution in pregnancy because of the possible hormonal effects.

PRACTICE POINTS/PATIENT COUNSELLING

- Hops is often used as a mild sedative in combination with other herbs such as valerian and passionflower.
- Several randomised trials have found that the combination of hops and valerian improve sleep quality, without next-day drowsiness; however, further investigation is required to determine the role of hops in achieving this effect.
- Although generally taken orally, it has also been successfully used as a bath additive and in aromatherapy pillows to induce sleep.
- It is traditionally used to treat anxiety, restlessness, pain, neuralgia and indigestion.
- It should not be used in patients with oestrogen-dependent tumours, and should be used with caution in pregnancy.

PATIENTS' FAQs

What will this herb do for me?

Hops may be a useful treatment for anxiety and restlessness, and when combined with other sedative herbs, such as valerian or passionflower, improves sleep quality without inducing next-day hangover effects.

When will it start to work?

Several doses may be required; however, effects are generally seen within 2 weeks.

Are there any safety issues?

Constituents in the herb appear to have some oestrogenic activity; therefore, people with oestrogen-dependent tumours should avoid its use.

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Horse chestnut

HISTORICAL NOTE The horse chestnut tree is commonly found in ornamental gardens throughout Europe, growing up to 35 metres tall. The seeds are not edible due to the presence of alkaloid saponins, but both the dried seeds and bark of the horse chestnut tree have been used medicinally since the 16th century. The seeds are also used for the children's game 'conkers' and were used to produce acetone during World Wars I and II. In modern times, a dry extract referred to as horse chestnut seed extract (HCSE) is standardised to contain 16–21% triterpene glycosides (anhydrous escin). HCSE has been extensively researched for its beneficial effects and is commonly used by general practitioners in Germany for the treatment of chronic venous insufficiency. Homoeopathic preparations of both the leaf and seed are also used for treating haemorrhoids, lower back pain and varicose veins, and the buds and flower are used to make the Bach flower remedies chestnut bud and white chestnut. The active component escin is also used intravenously and topically in cosmetics (Bombardelli et al 1996, Herbalgram 2000, PDRHealth 2006).

OTHER NAMES

Aescule, buckeye, chestnut, Castaño de Indias, graine de marronier d'inde, escine, eschilo, hestekastanje, hippocastani semen, marron europeen, marronnier, roßkastaniensamen, Spanish chestnut

BOTANICAL NAME/FAMILY

Aesculus hippocastanum (family [Sapindaceae] Hippocastanaceae).

It should be differentiated from *A. chinensis*, *A. turbinata*, *A. indica*, *A. californica* and *A. glabra*.

PLANT PARTS USED

Seed. Less commonly bark, flower and leaf.

CHEMICAL COMPONENTS

Horse chestnut seed contains 3–6% escin (aescin), a complex mixture of triterpene saponins (including the triterpene oligoglycosides escins Ia, Ib, IIa, IIb and IIIa) (Yoshikawa et al 1996), the acylated polyhydroxyoleanene triterpene oligoglycosides escins IIIb, IV, V and VI and isoescins Ia, Ib and V (Yoshikawa et al 1998), and the sapogenols hippocaesculin and barringtogenol-C (Konoshima & Lee 1986), flavonoids (including flavonol oligosides of quercetin and kaempferol) (Hubner et al 1999), condensed tannins, quinines, sterols (including stigmasterol, alpha-spinasterol, and beta-sitosterol) (Senatore et al 1989), sugars (including glucose, xylose and rhamnose) (Hubner et al 1999), and fatty acids (including linolenic, palmitic and stearic acids) (Herbalgram 2000). It also contains the toxic glycoside esculin (aesculin), a hydroxycoumarin that may increase bleeding time due to antithrombin activity (NMCD 2006).

Horse chestnut bark and flowers also contain the sterols stigmasterol, alpha-spinasterol and beta-sitosterol (NMCD 2006).

Although the majority of trials in the scientific literature have focused on the benefits of the HCSE extract, some authors suggest that the flavonoids contained in *A. hippocastanum* may provide additional benefits (Mills & Bone 2000).

MAIN ACTIONS

The major benefits of *A. hippocastanum* are related to its ability to prevent the degradation of vascular walls, maintaining vascular integrity and in turn preventing vascular hyperpermeability and the resulting oedema.

Vasoprotective/normalises vascular permeability

Horse chestnut appears to prevent the activation of leukocytes and therefore inhibit the activity of lysosomal enzymes (hyaluronidase and possibly elastase) involved in the degradation of proteoglycan (the main component of the extravascular matrix), thus reducing the breakdown of mucopolysaccharides in vascular walls (Pittler & Ernst 2004). Escin is the major constituent thought to be responsible for the inhibitory effects on hyaluronidase. Interestingly, ruscogenins found in *Ruscus aculeatus* L. (butcher's broom), while ineffective on hyaluronidase activity, exhibit significant anti-elastase activity (Facino et al 1995), which may explain the practice by many herbalists of combining the two herbs.

By reducing degradation, the synthesis of proteoglycans is able to occur, which reduces capillary hyperpermeability, preventing the leakage of fluid into intercellular spaces that results in oedema. The anti-exudative activity appears to be mediated by PGF_{2alpha} (Berti et al 1977). In animal studies the escins Ia, Ib, IIa and IIb have been shown to reduce capillary hyperpermeability induced by histamine, ascetic acid, carrageenan and serotonin (Guillaume & Padioleau 1994, Matsuda et al 1997). In experimental rat aortic-ring models, escin has been shown to increase endothelial cell permeability to calcium, which enhances the production of nitric oxide

(NO) (due to the effect of endothelial NO synthase, a calcium-dependent enzyme), and results in enhanced endothelium-dependent relaxation. This is thought to contribute to escin's beneficial effect in the treatment of venous insufficiency (Carrasco & Vidrio 2007).

A. hippocastanum promotes the proliferation behaviour of human endothelial cells in vitro in a dose-dependent manner (Fallier-Becker et al 2002) and may therefore also play a role in maintaining as well as protecting vascular walls.

By improving vascular tone, horse chestnut standardised extract (HCSE) may improve the flow of blood back to the heart, as demonstrated in animal studies in which it significantly increased, within normal arterial parameters, femoral venous pressure and flow, as well as thoracic lymphatic flow (Guillaume & Padioleau 1994).

Anti-oedema

By inhibiting the degradation of vascular walls, horse chestnut prevents the excessive exudation of fluid through the walls of the capillaries that would result in oedema. In animal experiments HCSE reduces oedema of both inflammatory and lymphatic origin (Guillaume & Padioleau 1994). Escin also appears to possess a weak diuretic activity (Mills & Bone 2000, NMCD 2006), which may support its anti-oedematous action.

Anti-inflammatory

Under experimental conditions, escin pre-treatment may reduce IL-6 release from vascular endothelium (Montopoli et al 2007). In animal studies the escins Ia, Ib, IIa and IIb have been shown to reduce capillary hyperpermeability induced by histamine, ascetic acid, carrageenan and serotonin (Guillaume & Padioleau 1994, Matsuda et al 1997). A sterol extract of horse chestnut bark was shown to have anti-inflammatory effects comparable to calcium phenylbutazone in a study of rats with carrageenan-induced paw oedema (Senatore et al 1989).

Antioxidant

HCSE dose-dependently inhibits both enzymatic and non-enzymatic lipid peroxidation in vitro (Guillaume & Padioleau 1994).

Chemopreventive, anti-angiogenic and anti-proliferative

Beta-escin has been shown to be a potent inhibitor of cell proliferation and inducer of apoptosis in HL-60 acute myeloid leukaemia cells (Niu et al 2008b) and human chronic myeloid leukaemia K562 cells (Niu et al 2008a); and inhibits the growth of colon cancer cells in rats (Patlolla et al 2006). Beta-escin sodium (40 micrograms/mL) induces endothelial cell apoptosis and inhibits endothelial cell proliferation in a dose-dependent manner (10, 20, 40 micrograms/mL) (Wang et al 2008).

OTHER ACTIONS

Animal studies have demonstrated that isolated escins Ia, Ib, IIa and IIb inhibit gastric emptying time and ethanol absorption, and exert a hypoglycaemic activity in the oral glucose tolerance test in rats (Matsuda et al 1999, Yoshikawa et al 1996).

Anti-ageing

A number of studies by Fujimura and others (2006a, 2006b, 2007) have suggested that horse chestnut extract can generate contraction forces in fibroblasts through stress fibre formation followed by activation of Rho protein and Rho kinase (Fujimura et al 2006b) and thus act as a potent anti-ageing factor. In a controlled trial of 40 women using an eye gel (3% horse chestnut extract) applied around the eyes three times a day for 9 weeks a significant reduction in wrinkle scores around the corners of the eye and lower eyelids was observed after 6 weeks (Fujimura et al 2006a, 2007).

CLINICAL USE

HCSE is chiefly used in chronic pathological conditions of the veins where there is increased activity of lysosomal enzymes resulting in damage to and hyperpermeability of vascular walls (Herbalgram 2000). Numerous pharmacological and clinical trials have confirmed the efficacy of HCSE in stabilising the walls of the venous system and improving conditions such as chronic venous insufficiency (Blekic 1996).

Chronic venous insufficiency

Horse chestnut has been used traditionally for the treatment of chronic venous insufficiency (CVI) and its associated symptoms, such as lower leg swelling. The ability of horse chestnut seed extract (HCSE) to inhibit the catalytic breakdown of capillary wall proteoglycans is thought in part to mediate this effect. Clinical trials in patients with chronic venous insufficiency and varicose veins have demonstrated a reduction in lower leg oedema and the subjective alleviation of leg pain, heaviness and itching (Suter et al 2006).

A recent Cochrane review that assessed 17 RCT of HCSE capsules (standardised to escin) concluded that signs and symptoms of CVI improve with HCSE as compared with placebo (Pittler & Ernst 2006). Six of seven placebo-controlled trials reported a significant reduction in leg pain for HCSE compared with placebo, another study reported a statistically significant improvement compared with baseline and one study reported that HCSE may be as effective as treatment with compression stockings. Pruritus was assessed in eight placebo-controlled trials. Four trials ($n = 407$) showed a statistically significant reduction compared with placebo and two trials showed a statistically significant difference in favour of HCSE compared with baseline, whereas one trial found no significant differences for a score including the symptom pruritus compared with compression. Meta-analysis of six trials ($n = 502$) suggested a reduction in leg volume compared with placebo, as did the studies in which the circumference at calf and ankle was assessed overall. Adverse events were usually mild and infrequent.

An earlier meta-analysis of 13 RCT ($n = 051$) and 3 observational studies ($n = 10,725$) found

that HCSE reduced leg volume by 46.4 mL (95% CI, 11.3–81.4 mL) and increased the likelihood of improvement in leg pain 4.1-fold (95% CI, 0.98–16.8), oedema 1.5-fold (95% CI, 1.2–1.9) and pruritus 1.7-fold (95% CI, 0.01–3.0). Observational studies reported significant improvements in pain, oedema and leg fatigue/heaviness (Siebert et al 2002).

A case observational study involving more than 800 GPs and more than 5,000 patients with CVI taking HCSE reported that symptoms of pain, tiredness, tension and swelling in the leg, as well as pruritus and tendency to oedema, all improved markedly or disappeared completely, with the additional advantage of better compliance than compression therapy (Greeske & Pohlmann 1996). In an open study carried out to assess the safety and tolerability of *A. hippocastanum*, 91 subjects received a tablet (equivalent to 50 mg escin) twice daily for 8 consecutive weeks. At the end of the study the majority of patients rated horse chestnut to be good or very good for Widmer stage I and II CVI (Dickson et al 2004).

In patients suffering from CVI, oedema can give rise to trophic skin changes, inflammatory lesions, and an increase in blood coagulability with the associated risk of thrombosis development. Therapy should therefore be aimed at providing protection against oedema at the earliest possible stage of venous disease (Widmer CVI stages I or II) to prevent complications (Pohlmann et al 2000). As HCSE therapy appears to provide more significant benefits in the earlier stages (less so with the advancement of the condition) (Ottillinger & Greeske 2001) it would appear prudent to initiate HCSE therapy early in order to prevent or delay the need for compression therapy, which is associated with discomfort and poor patient compliance. In the later stages combined treatment with compression stockings and HCSE may provide added benefit (Blaschek 2004, Pittler & Ernst 2004).

Although the standard dose used in clinical trials appears to be equivalent to 50 mg escin twice daily, one study observed that reducing the dose to 50 mg escin once daily at 8 weeks appeared to maintain similar benefits to the twice daily routine at the end of the 16-week observation period (Pohlmann et al 2000).

Venous leg ulceration

Chronic venous leg ulceration (VLU) is a common recurrent problem in the elderly population and may result in immobility, with 45% of patients being housebound (Baker & Stacey 1994). As a result, individuals with VLU frequently experience depression, anxiety, social isolation, sleeplessness and reduced working capacity (Leach 2004). CVI, which is characterised by an increase in capillary permeability, inflammatory reactions, decreased lymphatic reabsorption, oedema and malnutrition of tissues, is a precursor to VLU. As HCSE increases venous tone while reducing venous fragility and capillary permeability, and possesses anti-oedematous and anti-inflammatory properties, it has been speculated that by improving microcirculation, ulceration may be delayed or prevented (Blaschek 2004).

In a prospective triple-blind randomised placebo-controlled trial, 54 patients with venous leg ulcers received HCSE ($n = 27$) or placebo ($n = 27$) for 12 weeks. At weeks 4, 8 and 12 the difference between groups in the number of healed leg ulcers and change in wound surface area, depth, volume, pain and exudate was not statistically significant. There was however a significant effect on the percentage of wound slough over time ($P = 0.045$) and on the number of dressing changes at week 12 ($P = 0.009$) (Leach et al 2006a). As a result, after taking into account the cost of HCSE, dressing materials, travel, staff salaries and infrastructure for each patient, this study determined a cost benefit for the addition of HCSE to conventional therapy of AU$95 in organisational costs, and AU$10 in dressing materials per patient (Leach et al 2006b). Further large scale trials are required to fully elucidate the potential use in practice.

Haemorrhoids

Horse chestnut is also used both orally and topically for the treatment of haemorrhoids. Although it has not been investigated for this indication, escin has been shown to significantly improve signs and symptoms according to a placebo-controlled double-blind study of 72 volunteers with haemorrhoids. Symptom relief was experienced by 82% of subjects compared with 32% for placebo, and swelling improved in 87% compared with 38% for placebo (Sirtori 2001). Symptom improvement required at least 6 days of treatment to become established and the dose used was 40 mg escin three times daily.

OTHER USES

Traditionally the seeds are used to treat conditions affecting the veins, including haemorrhoids, phlebitis and varicose veins; bruising, diarrhoea, fever, enlarged prostate, eczema, menstrual pain, painful injuries, sprains, swelling and spinal problems. The leaf is used for soft tissue swelling from bone fracture and sprains, complaints after concussion, cough, arthritis and rheumatism, and the bark for malaria and dysentery, and topically for SLE and skin ulcers (NMCD 2006, PDRHealth 2006).

There is some evidence to support its use for preventing post-operative oedema (Sirtori 2001) and the antioxidant, vascular toning and anti-inflammatory effects of *A. hippocastanum*, as well as the presence of flavonoids and other active constituents, may support some of the other traditional uses (Wilkinson & Brown 1999).

Bell's palsy

Sodium beta-escin has been proposed as a potential agent for treating oedema complicated by Bell's palsy due to its ability to relieve tissue oedema, recover vasopermeability and eliminate pressure caused by oedema (Liu et al 2008).

DOSAGE RANGE

- Chronic venous insufficiency: HCSE standardised to 50–100 mg escin twice daily. The dose may be reduced to a maintenance dose of 50 mg escin once daily after 8 weeks (Pohlmann et al 2000).
- Australian manufacturers recommend 2–5 mL/day of 1:2 liquid extract.
- 1–2 g dried seed daily (Mills & Bone 2005).

ADVERSE REACTIONS

According to clinical trials *A. hippocastanum* and HCSE appear to be well tolerated with only mild, infrequent reports of adverse reactions including gastric irritation, skin irritation, dizziness, nausea, headache and pruritus. Postmarketing surveillance reports adverse effects of 0.7% (Micromedex 2003, NMCD 2006, PDRHealth 2006, Pittler & Ernst 2004, Siebert et al 2002).

Horse chestnut contains a toxic glycoside esculin (aesculin), a hydroxycoumarin that may increase bleeding time because of its antithrombin activity and may be lethal when the raw seeds, bark, flower or leaves are used orally. Poisoning has been reported from children drinking tea made with twigs and leaves (NMCD 2006).

Symptoms of overdose include diarrhoea, vomiting, reddening of the face, severe thirst, muscle twitching, weakness, loss of coordination, visual disturbances, enlarged pupils, depression, paralysis, stupor and loss of consciousness (NMCD 2006, PDRHealth 2006).

Horse chestnut can also cause hypersensitivity reactions, which occur more commonly in people who are allergic to latex (Diaz-Perales et al 1999).

Isolated cases of kidney and liver toxicity have occurred after intravenous and intramuscular administration (Micromedex 2003, Mills & Bone 2005, NMCD 2006).

SIGNIFICANT INTERACTIONS

In vitro studies have revealed that horse chestnut may inhibit CYP3A4 mediated metabolism and P-glycoprotein efflux transport activity (Hellum & Nilsen 2008). The clinical significance of these findings remains to be tested.

Antiplatelet/ anticoagulant medications

Properly prepared HCSE should not contain esculin and should not carry the risk of antithrombin activity — observe. Clinical significance unclear.

Hypoglycaemic agents

Due to possible hypoglycaemic activity, blood glucose levels should be monitored when horse chestnut or HCSE and hypoglycaemic agents are used concurrently (Yoshikawa et al 1996) — observe. Clinical significance unclear.

CONTRAINDICATIONS AND PRECAUTIONS

As saponins may cause irritation to the gastric mucosa and skin, *A. hippocastanum* should be taken with food, should not be applied topically to broken or ulcerated skin and should be avoided by people with infectious or inflammatory conditions of the gastrointestinal tract, including coeliac disease and malabsorption disorders.

PRACTICE POINTS/PATIENT COUNSELLING

- Horse chestnut extract has been extensively researched for its beneficial effects and is commonly used by GPs in Germany for the treatment of CVI. There is strong evidence to support its use for this indication.
- In practice, a dry extract is used (HCSE standardised to contain 16–21% triterpene glycosides (anhydrous escin)).
- HCSE is also used for venous leg ulceration because it increases venous tone while reducing venous fragility and capillary permeability, and possesses anti-oedematous and anti-inflammatory properties.
- HCSE is also used in the treatment of haemorrhoids. Although it has not been investigated for this indication, escin has been shown to significantly improve signs and symptoms under double-blind study conditions.
- HCSE is well tolerated with only mild, infrequent reports of adverse reactions including gastric irritation, skin irritation, dizziness, nausea, headache and pruritus.
- Horse chestnut can cause hypersensitivity reactions, which occur more commonly in people who are allergic to latex.

Horse chestnut flower, raw seed, branch bark or leaf may be toxic and are not recommended (Tiffany et al 2002).

Avoid use in the presence of hepatic or renal impairment (Micromedex 2003, NMCD 2006, PDRHealth 2006).

In toxicity studies in rats, escin decreased white blood cells, increased the number of red blood cells and platelets, and haemoglobin content; and reduced prothrombin time and thrombin time (5, 10, 15 mg/kg) (Li et al 2006).

PREGNANCY USE

Safety in pregnancy and lactation has not been well established.

PATIENTS' FAQs

What will this herb do for me?

Horse chestnut standardised extract (HCSE) will relieve signs and symptoms of chronic venous insufficiency such as pain, pruritus and oedema. It may also be of benefit in alleviating signs and symptoms in people with haemorrhoids and has been used in venous leg ulceration.

When will it start to work?

Beneficial effects in chronic venous insufficiency have been reported within 3–6 weeks; however, 12 weeks may be required in some cases. Escin provided symptom relief in haemorrhoids after 6 days of treatment.

Are there any safety issues?

HCSE is well tolerated with only mild, infrequent reports of adverse reactions including gastric irritation, skin irritation, dizziness, nausea, headache and pruritus. It can cause hypersensitivity reactions, which occur more commonly in people who are allergic to latex.

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Horseradish

HISTORICAL NOTE Horseradish is a commonly used spice with a long history of use in traditional medicine. The leaves are used in cooking and as a salad green. Horseradish is one of the 'five bitter herbs' of the biblical Passover.

COMMON NAME
Horseradish

OTHER NAMES
Amoraciae rusticanae radix, great mountain root, great raifort, mountain radish, pepperrot, red cole

BOTANICAL NAME/FAMILY
Armoracia rusticana, synonym *Armoracia lopathifolia*; *Cochlearia armoracia*, *Nasturtium armoracia*, *Roripa armoracia* (family Brassicaceae [Cruciferae])

PLANT PARTS USED
Fresh or dried roots and leaves

CHEMICAL COMPONENTS
Horseradish root contains volatile oils: glucosinolates (mustard oil glycosides); gluconasturtiin and sinigrin (S-glucosides); coumarins (aesculetin, scopoletin); phenolic acids, including caffeic acid derivatives and hydroxycinnamic acid derivatives, ascorbic acid; asparagin; resin; and peroxidase enzymes. Horseradish is one of the richest plant sources of peroxidase enzymes, which are commonly used as oxidising agents in commercial chemical tests.

MAIN ACTIONS
Horseradish is widely known for its pungent burning flavour. The pungency of horseradish is due to the release of allyl isothiocyanate and butyl thiocyanate upon crushing (Yu et al 2001). These mustard oil glycosides may irritate the mucous membranes upon contact or inhalation and may act as circulatory and digestive stimulants; however, the mechanism of action has not been fully elucidated (Blumenthal et al 2000, Jordt et al 2004). It has been found that topical application of allyl isothiocyanate to the skin activates sensory nerve endings producing pain, inflammation and hypersensitivity to thermal and mechanical stimuli due to depolarising the same sensory neurons that are activated by capsaicin and tetrahydrocannabinol (THC) (Jordt et al 2004). Allyl isothiocynate is known to have antimicrobial and antitumour properties (Pengelly 1996).

Circulatory stimulant
The mustard oils released when horseradish is crushed may be responsible for this activity.

Digestive stimulant
Again, it is suspected that the mustard oils may be responsible as these act as irritants. Large doses may cause emesis (Pengelly 1996).

OTHER ACTIONS
Isothiocyanates may inhibit thyroxine formation and be goitrogenic (Langer 1965), although this has not been demonstrated clinically.

The peroxidase enzymes assist in wound healing, whereas the sulfur-containing compounds may decrease the thickness of mucus by altering the structure of its mucopolysaccharide constituents (Mills & Bone 2000). Antispasmodic and antimicrobial effects have also been reported (Blumenthal et al 2000, Newell et al 1996). Horseradish has been found to lower plasma cholesterol and faecal bile acid excretion in mice fed with a cholesterol-enriched diet possibly due to interference with exogenous cholesterol absorption (Balasinska et al 2005).

Horseradish has also been found to contain compounds that inhibit tumour cell growth and COX-1 enzymes (Weil et al 2005). In vivo trials testing a combination of herbs, including horseradish, has been found to protect against viral transmission of avian influenza (Oxford et al 2007).

CLINICAL USE
The therapeutic effectiveness of horseradish has not been significantly investigated.

Nasal congestion and sinusitis
Horseradish is widely used in combination with other ingredients such as garlic in herbal decongestant formulations. Anecdotal evidence suggests that a mild, transient decongestant effect occurs. It is reputed to eliminate excessive catarrh from the respiratory tract (Drew 2002, Tancred 2006), although clinical research is not available to confirm its efficacy.

OTHER USES
It has been used traditionally to treat both bronchial and urinary infections, joint and tissue inflammations, as well as treating gall bladder disorders, reducing oedema and as an abortifacient (Skidmore-Roth 2001).

An in vivo study in mice demonstrated that allyl isothiocyanate markedly inhibited the formation of gastric lesions (Matsuda et al 2007).

DOSAGE RANGE
- The typical dose of horseradish is 2–20 g/day of the root or equivalent preparations.
- Topical preparations with a maximum of 2% mustard oil content are commonly used (Blumenthal et al 2000).

ADVERSE REACTIONS
Despite the potential for severe irritation, horseradish is generally recognised as safe for human consumption in quantities used as food. Consuming large amounts of horseradish can cause gastrointestinal upset, vomiting and diarrhoea, and

irritation of mucous membranes. Skin contact with fresh horseradish can cause irritation and blistering or allergic reactions. If used topically it should be diluted 50% with water and not applied for prolonged periods. Application to a small test area before wider application is recommended for people with sensitive skin.

SIGNIFICANT INTERACTIONS

None known.

CONTRAINDICATIONS AND PRECAUTIONS

Internal use should be avoided in people with stomach and intestinal ulcers and kidney disorders, as well as in children under the age of 4 years (Blumenthal et al 2000).

Traditionally, horseradish is considered a warming herb that will exacerbate any 'hot' condition and is specifically indicated for 'cold' conditions.

PREGNANCY USE

The mustard oils released upon crushing are potentially toxic, therefore doses exceeding dietary intakes are contraindicated (Newell et al 1996).

PRACTICE POINTS/PATIENT COUNSELLING

- Horseradish has been used as a vegetable, condiment, diuretic and treatment for bronchial and urinary infections, joint and tissue inflammation and swelling.
- It is widely used together with other herbal ingredients such as garlic, as a decongestant in the treatment of colds and sinusitis.
- No scientific investigation has been undertaken to support its use, although anecdotal evidence suggests that it may be useful.
- Horseradish is generally safe when the root is ingested in usual dietary amounts, although excessive intake may cause irritation to the stomach, respiratory tract and kidneys.

PATIENTS' FAQs

What will this herb do for me?

Anecdotal evidence suggests that it may have decongestant effects and is a very popular treatment when combined with other herbs such as garlic, to relieve the symptoms of colds and sinusitis.

When will it start to work?

It may relieve symptoms within the first few doses, but scientific tests are not available to confirm this.

Are there any safety issues?

Horseradish can be quite irritating for some people due to its bitter and pungent characteristics.

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Iodine

BACKGROUND AND RELEVANT PHARMACOKINETICS

Iodine is an essential trace element required for proper functioning of the thyroid gland. It is mainly consumed as iodide salts obtained from sea salt, shellfish and seawater fish and vegetables, which are more bioavailable than the organic forms. The iodine content of soil is considered to be one of the most variable of all minerals, influenced by local geography and the type and quantity of fertiliser used in agriculture (Groff et al 2009). There is evidence of iodine-deficient soils in many regions of Australia. Dietary iodine content is also significantly influenced by agricultural iodine-containing compounds, used in irrigation products, fertilisers and livestock feeds (Zimmermann et al 2008).

Iodide is rapidly absorbed from the stomach to the small intestine and distributed via the blood to a range of tissues, most notably the thyroid, which traps iodide through an ATP-dependent iodide pump called the sodium iodide symporter. The thyroid contains 80% of the body's iodine pool, which is approximately 15 mg in adults. Also found in high concentrations in the salivary, gastric and mammary glands (exclusively during pregnancy and lactation in the latter), iodine's uptake is regulated by thyroid-stimulating hormone (TSH) (Groff et al 2009, Kohlmeier 2003).

Excreted via the kidneys when the needs of the thyroid have been met and an excess remains (Kohlmeier 2003), urine concentrations reflect plasma levels and have been used since the middle

of the 20th century to assess iodine status. Interestingly, there is no renal conservation mechanism for this mineral and the only evidence of iodine preservation comes from the scavenging and recycling of thyroid hormones by the selenium-dependent deiodinase DII (Kohlmeier 2003). Of the total amount excreted, 20% occurs via faeces and additional losses can occur through sweat, which, although a minor eliminatory pathway under normal circumstances, can be a significant contributor for people living in hot climates with low dietary consumption (Groff et al 2009).

FOOD SOURCES

Iodine can occur in foods as either an inorganic or organic salt, or as thyroxine in animal sources. Unlike many other essential nutrients, the organic form of iodine found in animal products has poor bioavailability, whereas the iodide salts found in the sea are almost completely absorbed (Jones 2002).

However, irrespective of whether it is animal or plant derived, food from the land has enormous variability in terms of iodine content, from 1 to 10 microgram/kg (Geissler & Powers 2005), due to iodine's high solubility and therefore susceptibility to leaching (Wahlqvist 2002).

Additionally, chemicals known as goitrogens are naturally found in some foods (e.g. brassica [cabbage] family) and these interfere with iodine utilisation and thyroid hormone production.

Best sources

Due to the high saltwater levels of bioavailable iodide, all sea-dwelling creatures, animal or plant, are considered as superior dietary sources.

- Seawater fish
- Shellfish
- Sea vegetables such as seaweeds
- Iodised salt (fortified form of table salt) — providing 20–40 microgram/g
- Commercially manufactured breads due to the iodate dough oxidisers
- Dairy milk (variable)

In Australia, milk no longer supplies a significant amount of iodine, whereas in the United Kingdom it is still an important dietary source because of the use of both supplemented feeds and iodine-based antiseptics in the dairy industry (Geissler & Powers 2005).

DEFICIENCY SIGNS AND SYMPTOMS

Primary deficiency

Iodine deficiency results when iodide intake is < 20 microgram/day (Kasper et al 2005). In situations of moderate deficiency, TSH induces thyroid hypertrophy in order to concentrate iodide, resulting in goitre. Most of these cases remain euthyroid, but in cases of severe iodine deficiency, myxoedema may result in adults and cretinism in infants, both of which are serious conditions.

Myxoedema is characterised by swelling of the hands, face, feet and peri-orbital tissues and can lead to coma and death if sufficiently severe and left untreated. Endemic cretinism is divided into two forms, neurologic or myxoedematous, depending on the interplay of genetics and iodine deficiency. Usually, children with neurologic cretinism are mentally deficient and often deaf mute but of normal height and strength and may have goitre. Myxoedematous cretinism is characterised by dwarfism, mental deficiency, dry skin, large tongue, umbilical hernia, muscular incoordination and puffy facial features. Concomitant selenium deficiency may be a contributing factor in myxoedematous cretinism. Early treatment with thyroid hormone supplementation can promote normal physical growth; however, intellectual disability may not be prevented and in very severe cases death may ensue.

The term 'iodine deficiency disorders' (IDD) has been coined to refer to the collection of health problems that result from iodine deficiency, ranging from the mild and common (e.g. goitre) to severe and life threatening (e.g. cretinism and myxoedema) (Groff et al 2009).

Although severe iodine deficiency is rare in Australia and New Zealand, many parts of the world have notoriously low iodine levels. Countries where iodine deficiency is a primary concern include China, Latin America, Southeast Asia and the eastern Mediterranean (Wahlqvist 2002). A report conducted by the World Health Organization in 2005 found that while many countries had succeeded in reaching optimal iodine nutrition through enhanced monitoring and fortification programs over the past decade, an estimated 285 million school-age children and close to 2 million adults worldwide still suffer from IDD (Andersson et al 2005).

Fetal deficiency

The fetus depends solely on maternal thyroid hormones during the first trimester of pregnancy (Soldin et al 2002) and iodine deficiency uncorrected prior to mid-gestation results in irreversible brain damage (de Escobar et al 2007). To accommodate for this, increasing plasma volume, renal clearance and the increased thyroid hormone degradation secondary to hyperactivity of the uterine–placental deiodinases, healthy pregnant women exhibit a surge in T_4 production, partly under the stimulation of human chorionic gonadotropin (HCG). From week 11 of gestation, fetal thyroid hormone synthesis usually begins, still dependent on maternal provision of iodine and at term a residual 20–40% of T_4 found in cord blood is of maternal origin (de Escobar et al 2008, Delange 2007, Glinoer 2007, Zimmermannn 2008). These demands necessitate a ≈ 100% increase (e.g. 250–300 microgram/day) (de Escobar et al 2008, Delange 2007) in iodine intake from conception. Should such needs go unmet, the mother will adapt by preferentially producing T_3 to stave off both clinical and biochemical hypothyroidism. The fetus, however, yet to develop rapid adaptations to circulating iodine levels, will exhibit reductions of all thyroid hormones and develop hypothyroidism in spite of the mother's euthyroid state (de Escobar et al 2008).

Adequate iodine and healthy functioning of both the maternal and the fetal thyroid glands play a critical role in fetal neuropsycho-intellectual development, due to its role in neuronal migration and myelination, with brain damage risk secondary to a deficiency, peaking in the second trimester and the early neonatal period. Studies have also confirmed that 'mild but measurable' psychomotor deficits in early childhood can result from subclinical hypothyroidism and hypothyroxaemia caused by mild-to-moderate iodine deficiency in pregnancy (Glinoer 2007, Soldin et al 2002). Finally, severe iodine deficiency during pregnancy also increases risk of stillbirths, miscarriage, perinatal mortality and congenital abnormalities (Zimmermann 2008).

Because of the severe neurological consequences of untreated congenital hypothyroidism, neonatal screening programs have been established in some developed countries; however, early or pre-pregnancy detection of subclinical iodine deficiency would be most effective (Ares et al 2008).

Premature infant deficiency

Premature infants face a significantly elevated risk of iodine deficiency secondary to a collusion of factors: interruption of maternal supply (small amounts of breast milk provide substantially smaller quantities of iodine than placental transfer), immaturity of the hypothalamic pituitary thyroid axis and the deiodinase systems, maternal antibodies and postnatal exposure to drugs (e.g. dopamine, heparin, corticosteroids) (Ares et al 2008). Research suggests that 75% of premature neonates demonstrate a negative iodine balance at 5 days post-partum prior to intentional repletion.

Secondary deficiency

High consumption of goitrogens can induce a secondary deficiency state. Goitrogens are substances that inhibit iodine metabolism and include thiocyanates found in the cabbage family (e.g. cabbage, kale, cauliflower, broccoli, turnips and Brussels sprouts) and in linseed, cassava, millet, soybean and competing entities, such as other members of the halogen family (e.g. bromine, fluorine and lithium, as well as arsenic) (Groff et al 2009). Most researchers agree, however, that moderate intake of goitrogens in the diet is not an issue, except when accompanied by low iodine consumption (Groff et al 2009, Kohlmeier 2003). A very rare cause of secondary iodine deficiency and hypothyroidism is TSH deficiency.

Low selenium intake

Low dietary intake of selenium is a factor that exacerbates the effects of iodine deficiency. Selenium is found in the thyroid gland in high concentrations, and while iodine is required for thyroid hormone synthesis, selenium-dependent enzymes are required for the peripheral conversion of thyroxine (T_4) to its biologically active form triiodothyronine (T_3) (Higdon 2003), as well as the general recycling of iodine. Selenium deficiency results in decreased T_4 catabolism, which leads to increased production of peroxide and thyroid cell destruction, fibrosis and functional failure.

SIGNS AND SYMPTOMS

Overall, in addition to highly visible goitre, moderate-to-severe iodine deficiency produces subtle but widespread effects secondary to hypothyroidism, including reduced educability, apathy and impaired productivity, culminating ultimately in poor social and economic development (Zimmermann 2008).

Mild hypothyroidism

This refers to biochemical evidence of thyroid hormone deficiency in patients who have few or no apparent clinical features of hypothyroidism.

Congenital hypothyroidism

The majority of infants appear normal at birth and < 10% are diagnosed with hypothyroidism based on the following clinical features:

- prolonged jaundice
- feeding problems
- hypotonia
- enlarged tongue
- delayed bone maturation
- umbilical hernia.

Importantly, permanent neurologic damage results if treatment is delayed.

Adult hypothyroidism

According to Beers (2005), the clinical signs of hypothyroidism in adults are as follows:

- weakness, tiredness and sleepiness
- dry skin
- cold intolerance
- hair loss and diffuse alopecia
- poor memory and difficulty concentrating
- constipation
- reduced appetite and weight gain
- dyspnoea
- hoarse voice
- increased susceptibility to infectious diseases
- increased susceptibility to cardiovascular diseases
- paraesthesia
- puffy hands, feet and face and peripheral oedema
- impaired hearing
- menorrhagia (later amenorrhoea)
- carpal tunnel and other entrapment syndromes are common, as is impairment of muscle function with stiffness, cramps and pain
- reduced myocardial contractility and pulse rate, leading to a reduced stroke volume and bradycardia.

In adults, mild–moderate iodine deficiency also results in higher rates of more aggressive subtypes of thyroid cancer and an increased risk of (non) toxic goitre (Zimmermann 2008).

MAIN ACTIONS

Thyroid hormone production

Iodine is essential for the manufacture of T_4 and T_3, which are hormones that influence growth, maturation, thermogenesis, oxidation, myelination of the CNS and the metabolism of all tissues (Jones

2002). The thyroid hormones, especially T_3, exert their effects by binding to nuclear receptors on cell surfaces, which in turn trigger binding of the zinc fingers of the receptor protein to the DNA (Groff et al 2009).

OTHER ACTIONS

Due to the concentration of appreciable iodine levels in a range of other tissues, including salivary, gastric and lactating mammary glands, and the ovaries, questions remain about potential additional actions of iodine. One hypothesis postulates iodine as an indirect antioxidant, via its capacity to reduce elevated TSH, a trigger of increased peroxide levels in the body (Smyth 2003).

CLINICAL USE

Increased iodine intake can be achieved through dietary modification and supplementation with tablets. Dietary modification usually refers to increased intake of iodised salt, but may also refer to use of iodised water, iodised vegetable oil or seafood.

Treatment and prevention of deficiency

Iodine deficiency is accepted as the most common cause of brain damage worldwide, with IDD affecting 740 million people (Higdon 2003). Although it is well accepted that severe deficiency is responsible, evidence is now emerging that mild deficiency during pregnancy is also important and can have subtle effects on brain development, lowering intellectual functioning and inducing psychomotor deficits in early childhood (Glinoer 2007). Preliminary data are also emerging to suggest an association between iodine deficiency hypothyroidism of pregnancy and the incidence of attention-deficit/hyperactivity disorder (ADHD) in the offspring; however, this still requires confirmation in larger studies (Soldin et al 2002, Vermiglio et al 2004).

Pregnancy

Severe iodine deficiency is uncommon in Western countries, such as Australia and New Zealand, but several local surveys have identified that mild-to-moderate deficiency is more prevalent than once thought. A research group at Monash Medical Centre in Melbourne screened 802 pregnant women and found that 48.4% of Caucasian women had urinary iodine excretion (UIE) concentrations below 50 microgram/L compared to 38.4% of Vietnamese women and 40.8% of Indian/Sri Lankan women (Hamrosi et al 2005). These figures are disturbing when the WHO defines healthy UIE levels as greater than 100 microgram/L, mild deficiency is diagnosed at 51–100 microgram/L and moderate-to-severe deficiency at < 50 microgram/L (Gunton et al 1999). A study conducted at a Sydney hospital involving 81 women attending a 'high' risk clinic found moderate-to-severe iodine deficiency in 18.8% of subjects and mild iodine deficiency in another 29.6% (Gunton et al 1999), the former clearly too close to the WHO maximum acceptable level of 20%. This study also revealed that almost 5% of the sample had UIE < 25 microgram/L. Based on such results, it may well be expected that endemic cretinism could emerge, with an overt manifestation possibly delayed due to low-to-moderate intake of goitrogens and adequate selenium levels in this population.

Aside from fortification programs in populations affected by severe iodine deficiency, there have been several RCTs of iodine supplementation in mild-to-moderately deficient pregnant women (Zimmerman 2008). While treatment effects include reductions in maternal and newborn thyroid size and, in some, reduced maternal TSH, none of the studies have demonstrated a positive effect on T_4 and T_3 of mother or child, or measured longer term clinical outcomes. Future research needs to address these issues.

Infants

An investigation of infant TSH levels within 72 h of birth at the Royal North Shore Hospital in Sydney suggests that endemic IDD may be emerging (McElduff 2002). Currently, the WHO recommends that less than 3% of newborns should have TSH levels greater than 5 mIU/L and of the 1773 infants enrolled in the study, 5–10% had a TSH reading > 5 mIU/L.

Children and adolescents

Evidence of iodine deficiency is not limited to pregnant women and newborns and has also been demonstrated in Australian schoolchildren (Li et al 2006). Iodine status in schoolchildren is based on median UIE values and is categorised as normal (UIE ≥ 100 microgram/L) or as mild (UIE 50–99 microgram/L), moderate (UIE 20–49 microgram/L) and severe deficiency (UIE < 20 microgram/L). The UIE is considered in combination with the child's sex, year of school and presence of goitre.

A study of Melbourne schoolchildren aged 11–18 years found that 76% (439/577) had abnormal UIE values, with 27% (156/577) possessing values consistent with moderate-to-severe iodine deficiency (McDonnell et al 2003). The median UIE value in girls was lower than that in boys (64 microgram/L vs 82 microgram/L), and girls had significantly lower UIE values overall ($P < 0.002$). A study of 324 schoolchildren aged 5–13 years from the Central Coast of New South Wales produced similar results and there was a median UIE concentration of 82 microgram/L, with 14% of children having levels below 50 microgram/L (Guttikonda et al 2003).

These findings were confirmed in the Australian National Iodine Nutrition Study, which identified inadequate iodine intake in the Australian population and called for the urgent implementation of mandatory iodisation of all edible salt in Australia (Li et al 2006). The study consisted of a survey of 1709 schoolchildren aged 8–10 years in the five mainland Australian States and was conducted between July 2003 and December 2004. It found that, overall, children in mainland Australia are borderline iodine deficient, with a national median UIE of 104 microgram/L. On a state basis, children in Victoria and New South T Wales are mildly iodine deficient,

Clinical note — Why is iodine deficiency on the rise?

In spite of increased rates of household iodised salt use globally since 1990, iodine intakes in Australia are falling (Zimmermann 2008). The emergence or re-emergence of iodine deficiency, however, is not limited to Australia; median UIE had declined by more than 50% between 1971 and 1994 in the United States (Gunton et al 1999, Zimmerman 2008).

Three reasons have been proposed to explain the emergence of iodine deficiency in developed countries. First, milk was traditionally viewed as a good dietary source of iodine; however, since the 1990s its iodine content has reduced significantly because iodine-containing sanitisers have been gradually replaced with chlorine-containing substitutes. The significance of this change within the dairy industry was recently shown by Li et al (2006) who compared the iodine content of Australian milk products from 1975 and 2004. They identified mean iodine concentrations of 593.5 microgram/L and 583 microgram/L from samples taken from Victoria and New South Wales (NSW), respectively in 1975 compared to a median concentration of 195 microgram/L in 2004 (250 mL providing 50–60 microgram iodine). Interestingly, the same researchers demonstrated that dairy products and water in northern and central Queensland contain higher iodine levels, which may explain the lower incidence of iodine deficiency in these areas (Li et al 2006). In spite of this, a survey of dietary habits of Tasmanian schoolchildren has revealed that consumption of dairy products is associated with improved iodine status (Hynes et al 2004), a case of some being better than none.

A second reason may relate to public health campaigns that have resulted in increased awareness of the potential adverse effects of salt and reduced its consumption, but failed to highlight the potential benefits of a moderate intake of iodised salt. In addition, few food manufacturers use iodised salt in their products, further reducing exposure to iodine (Gunton et al 1999).

Lastly, the mineral depletion of soils is another possible contributing factor, in particular, the depletion of selenium. Considering its role in iodine utilisation, selenium deficiency would potentiate the effects of iodine deficiency. Other theoretical considerations include increased environmental exposure to halogens, such as fluorine and chlorine, and increased consumption of goitrogens, such as soy, in the diet.

Although identifying the key factors responsible for the growth of iodine deficiency is important (Thomson 2004), many authors argue that implementation of national iodine monitoring and surveillance of the iodine content in foods are the most immediate concern (Li et al 2006, McDonnell et al 2003). Lessons learnt from Tasmania's iodine supplementation program, where statewide bread fortification failed to reduce the prevalence of iodine deficiency in children, indicate that greater efforts are required to create significant improvements in iodine status.

with median UIE levels of 89 microgram/L and 73.5 microgram/L, respectively, South Australian children are borderline iodine deficient, with a median UIE of 101 microgram/L, whereas both Queensland and Western Australian children are iodine sufficient, with median UIE levels of 136.5 microgram/L and 142.5 microgram/L, respectively. Researchers attributed the decline in iodine intake to changes within the dairy industry, with chlorine-containing sanitisers now replacing iodine-containing sanitisers and decreased intake of iodised salt.

In 2001, an iodine supplementation program was initiated in Tasmania because it was identified as an area of endemic goitre by the Department of Health Services. The program involves the use of iodised salt in 80% of Tasmania's bread production and aims to reduce the incidence of iodine deficiency. Despite encouraging preliminary data (Doyle & Seal 2003), iodine levels are still inadequate according to the WHO standards. There have been conflicting opinions about the success of this program, with the largest study demonstrating evidence of ongoing iodine deficiency (Seal et al 2003, Guttikonda et al 2002).

Iodine deficiency in children and adolescents is associated with poorer school performance, reduced achievement motivation and a higher incidence of learning disabilities (Tiwari et al 1996, Zimmermann 2008). A meta-analysis of 18 studies from eight countries of people aged between 2 and 30 years showed that iodine deficiency alone reduced mean IQ scores by 13.5 points in children (Bleichrodt et al 1996). Iodine repletion studies in children have yielded improved somatic growth, partial reversal of cognitive impairment and normalisation of age of onset of puberty; however, the strength of the evidence is hampered by methodological issues (Markou et al 2008, Zimmermann et al 2006, Zimmermann 2008).

Adults

A study of non-pregnant adults in 1999 demonstrated iodine deficiency in 26.3% of 'healthy' subjects and 34.1% of diabetic subjects (Gunton et al 1999).

Non-toxic goitre thyroidectomy

One 12-month study involving 139 patients who had undergone thyroidectomy for non-toxic goitre identified that supplementing L-thyroxine therapy with iodised salt produced significant improvements in thyroid function compared with stand alone L-thyroxine therapy (Carella et al 2002).

OTHER USES

Prevention of attention-deficit hyperactivity disorder

Emerging data from research conducted over the past 15 years suggest a possible link between low maternal iodine status and increased risk of

ADHD in the offspring. According to a report published in 2004, 11 of 16 children born to women living in a moderately iodine-deficient region in Italy developed ADHD compared to no offspring from the 11 control mothers living in a marginally iodine-deficient region (Vermiglio et al 2004).

On the other hand, another group of researchers investigated whether T_4 levels at birth could represent a biomarker for later development of ADHD and found that all newborns in the sample had T_4 within the normal range and no correlation between values and risk could be demonstrated (Soldin 2002, Soldin et al 2003). This evidence invalidated TSH levels as a biomarker of risk, but does not disprove a link between iodine and ADHD, as earlier studies found that those newborns who later developed ADHD were all euthyroid at birth (Vermiglio et al 2004).

Although further investigation is required to clarify these observations, they have provided a new avenue for ADHD research.

Fibrocystic breast disease and cyclic mastalgia

A 1993 review that focused on three clinical studies suggests that iodine supplementation may improve objective and subjective outcomes, including pain and fibrosis, for women with fibrocystic breast disease and cyclic mastalgia (Ghent et al 1993). Together the trials involved 1000 women and used a variety of different forms, the most successful being molecular iodine at a dose of 0.08 mg/kg (approximately equivalent to 500 microgram/day in a 60 kg woman) (Ghent et al 1993).

Recently, a placebo-controlled trial conducted with 11 euthyroid women with cyclic mastalgia tested different doses of molecular iodine ranging from 1.5 to 6 mg/day and showed that after 3 months of treatment, 50% of patients consuming 3 or 6 mg/day experienced a significant decrease in pain (Kessler 2004). Although no dose-related adverse events were detected, further investigation is required to confirm both efficacy and safety.

Breast cancer

There is suggestive evidence of a preventive role for iodine in breast cancer. As far back as 1896, research has suggested a link between iodine deficiency, thyroid disease and breast cancer (Gago-Dominguez & Castelao 2008, Smyth 2003, Stoddard et al 2008). Epidemiological data have demonstrated a correlation between increased incidence of breast cancer and a range of thyroid conditions, most notably hypothyroidism, with both conditions demonstrating peak incidence in postmenopausal women (Gago-Dominguez & Castelao 2008, Smyth 2003). A prospective study of peri- and postmenopausal women revealed that low free T_4 was an independent risk for the development of breast cancer (OR 2.3). Another study found that the premenopausal women treated for differentiated thyroid cancer with radioactive iodine were at an increased risk of developing breast cancer over the following 5–20 years (Gago-Dominguez & Castelao 2008). In addition, the observed low rates of breast cancer in Japanese women consuming a traditional diet are speculated to be partly due to a high dietary iodine intake, further suggesting a protective effect (Patrick 2008). Notably, this protection disappears when Japanese women consume a 'Western diet'.

It is noteworthy that both the thyroid and the breast share the capacity to concentrate iodide, which exerts both an oxidant effect, triggering and facilitating apoptosis and antioxidant effect, protecting cells from peroxidative damage (Gago-Dominguez & Castelao 2008, Venturi 2001) and converts it to iodine. The thyroid retains this capacity throughout life, whereas the healthy breast can only concentrate iodide during pregnancy and lactation, states associated with a reduced risk of breast cancer. Curiously, ≈ 80% of breast cancers also demonstrate iodide uptake (Stoddard et al 2008). It has been theorised that with iodine insufficiency during pregnancy and lactation, the protective effect of iodide may be compromised, concomitant with diminished oxidant and antioxidant activities. Researchers speculate that this scenario may be compounded by co-existing selenium deficiency (Turken et al 2003).

Besides the diminished antioxidant effect, studies with animal models show that iodine deficiency results in changes in the mammary gland that makes it more sensitive to the effects of oestradiol (Stoddard et al 2008, Strum 1979). Iodine has been implicated in the synthesis of alpha-oestrogen receptors, down-regulation of several oestrogen-responsive genes and increased expression of the cytochrome P450 genes responsible for its phase I detoxification (Stoddard et al 2008). Together with other sources of evidence, it is clear that the potential protective effect of iodine against breast cancer is independent of its thyroid role (Stoddard et al 2008).

At present, the only interventional evidence comes from rat studies, demonstrating that administration of Lugol's iodine or iodine-rich Wakame seaweed suppressed the development of induced mammary tumours (Funahashi et al 2001) and in vitro evidence confirming that molecular iodine induces apoptosis in breast cancer cell lines (Shrivastava et al 2006). In light of ongoing evidence of a superior effect of molecular iodine rather than iodide in relation to breast pathology in both animals and humans, rigorous human studies using this form are required (Patrick 2008, Stoddard et al 2008).

Water purification

Iodine-releasing tablets and iodine tincture have been used for many years to decontaminate water and have been used by the United States Army since World War II. A weak aqueous solution of 3–5 ppm of elemental iodine can destroy a wide range of enteroviruses, ameobae and their cysts, bacteria and their spores, as well as algae. Under temperate conditions of 25°C the disinfection process takes 15 minutes, longer in colder conditions. Adding to the versatility of iodine as a water decontamination agent is its ability to act over a wide range of pH and still be effective in the presence of

ammonia and amino ions from nitrogenous wastes that may be also present in the water (Kahn & Visscher 1975).

Antiseptic

Iodine solution is widely used as a topical antiseptic in the treatment of superficial wounds. It is a highly effective method of decontaminating intact skin and minor wounds and has a low toxicity profile. Povidone–iodine preparations have replaced older iodine solutions and are now the most widely used form.

Although the treatment is considered safe, a number of reports of iodine toxicity in newborns receiving ongoing treatment with topical iodine-based solutions suggest that it should be used with caution as an ongoing treatment in this group and TSH monitoring considered where appropriate.

DOSAGE RANGE

Australian recommended daily intake (RDI)

- Infants
  - 0–6 months: 90 microgram/day.
  - 7–12 months: 110 microgram/day.
- Children
  - 1–3 years: 90 microgram/day.
  - 4–8 years: 90 microgram/day.
  - 9–14 years: 120 microgram/day.
  - >14 years: 150 microgram/day.
- Adults: 150 microgram/day.
- Pregnancy: 220 microgram/day.
- Lactation: 270 microgram/day.
- Upper level of intake
  - 1–3 years: 200 microgram/day.
  - 4–8 years: 300 microgram/day.
  - 9–13 years: 600 microgram/day.
  - 14–18 years (including pregnancy, lactation): 900 microgram/day.
  - Adults >18 years (including pregnancy, lactation): 1100 microgram/day.

These are the newly revised Australian RDIs, which are more closely aligned with the WHO recommendations than previously.

According to clinical studies

- ADHD prevention: adequate intake to prevent maternal deficiency (approximately 250 microgram/day).
- Fibrocystic breast disease and cyclic mastalgia: 500 microgram–6 mg molecular iodine/day.
- Breast cancer prevention: dose is unknown; however, it is suggested that women meet RDI to prevent deficiency.
- Water disinfectant: 3–5 ppm in water or eight drops of 2% tincture to approximately 1 L of water.

TOXICITY

Chronic iodine toxicity results when iodide intake is approximately 2 mg daily or greater (Beers 2005). Overconsumption of iodine can cause gastrointestinal irritation, abdominal pain, nausea, vomiting and diarrhoea, cardiovascular symptoms and can induce both hypo- and hyperthyroidism, depending on the patient's preexisting susceptibility (Wahlqvist 2002, Zimmermann 2008). Excess iodine during pregnancy has also been associated with increased risk of postpartum thyroiditis (Guan et al 2005). Alternatively, there are many cases in which excesses have been tolerated without any overt consequences, particularly in individuals with healthy thyroid function (Geissler & Powers 2005, Groff et al 2009, Zimmermann 2008). Chronic ingestion of ≥ 500 microgram/day by children has resulted in increased thyroid size (Zimmermann 2008). Intake of very high doses can lead to a brassy taste in the mouth, increased salivation, gastric irritation and acneiform skin lesions.

SIGNIFICANT INTERACTIONS

Goitrogens

These are substances that interfere with iodine utilisation or thyroid hormone production and include thiocyanates found in the cabbage family (e.g. cabbage, kale, cauliflower, broccoli, turnips and Brussels sprouts) and in linseed, cassava, millet and soybean — separate intake of iodine and goitrogens where possible. Smoking has also been shown to increase thiocyanate levels and reduce iodine content in the breastmilk of smoking mothers (Zimmermann et al 2008). Other chemical goitrogens include perchlorate and disulphides, the latter from coal processes and there is accumulating evidence of thyroid endocrine disruptors in the form of ingredients used in cosmetics, as pesticides or plasticisers. Major targets are the sodium–iodide symporter (NIS), the hemoprotein thyroperoxidase (TPO), the T_4 distributor protein transthyretin (TTR) and the deiodinases (Köhrle 2008).

Soy

The actions of this particular goitrogen are two-fold: ingestion of soy appears to inhibit iodine absorption to some extent (particularly when presented in its thyroxine form in the gut) and also high levels of the isoflavones, genistein and daidzein, can inhibit T_3 and T_4 production — separate intake of iodine and goitrogens where possible. Particular attention should be paid to minimising soy consumption in individuals taking thyroid hormone supplementation, as it has been shown that soy consumption can increase dosage requirements.

Selenium

Selenium is intrinsic to the metabolism and activity of the thyroid hormones, facilitating the conversion of T_4 to T_3 and is also responsible for the only iodine recycling pathway of the body through the action of the deiodinases on excess or unnecessary thyroid hormones to release the iodine — beneficial interaction.

CONTRAINDICATIONS AND PRECAUTIONS

Thyroid conditions

Due to the complex and diverse causes of thyroid conditions, it is advised that iodine supplementation should be avoided unless under the supervision of a medical practitioner.

PRACTICE POINTS/PATIENT COUNSELLING

- Iodine is an essential trace element required for healthy functioning of the thyroid gland and for normal growth and development.
- It is mainly consumed as iodide salts from sea salt, shellfish, seawater fish and vegetables.
- Iodine is essential for the manufacture of thyroxine (T_4) and liothyronine (T_3), which are hormones that influence growth, maturation, thermogenesis, oxidation, myelination of the CNS and the metabolism of all tissues (Jones 2002).
- Iodine supplementation is commonly used to prevent and treat deficiency. There is also some evidence that it may reduce pain in fibrocystic breast disease and cyclic mastalgia and suggestive evidence of a protective role against breast cancer; however, rigorous research is required to confirm these observations.
- Current evidence points to widespread mild-to-moderate iodine deficiency in Australia, suggesting that dietary intake is inadequate and supplementation or fortification of foods with additional iodine may be required.

PREGNANCY USE

Up until 2006, the Australian recommended daily intake of iodine was 150 microgram for pregnant women and 170 microgram for lactating women; however, reflecting new research, the Australian RDI levels for pregnancy have been revised and increased. Care should be taken to avoid ingestion of excessive amounts during pregnancy due to suspected links with increased rates of postpartum thyroiditis and other disorders of thyroid function (Guan et al 2005).

PATIENTS' FAQs

What will this supplement do for me?

Adequate intake of iodine is critical for healthy thyroid function and normal growth and development. Ensuring adequate intake becomes critical during pregnancy and breastfeeding when the infant is solely dependent on the mother's intake for normal growth and brain development. Currently, there is some suggestive evidence that adequate iodine particularly during the female reproductive years may be protective against breast cancer and supplementation may relieve symptoms of breast pain in fibrocystic breast disease and cyclic mastalgia.

When will it start to work?

The time frames depend on the indication it is being used to treat and the level of deficiency. In the case of breast pain, studies suggest that 3 months of treatment are required to attain significant symptom relief.

Are there any safety issues?

People with preexisting thyroid conditions should only increase iodine intake under professional supervision. Doses in excess of the RDI should be avoided unless under the supervision of a medical practitioner.

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Iron

BACKGROUND AND RELEVANT PHARMACOKINETICS

Iron is an essential mineral found in the body in haem or non-haem form. The average human body contains 2–4 g of iron. Although the metal exists in several oxidation states in nature, only the ferrous (Fe^{2+}) and ferric (Fe^{3+}) forms are stable in the aqueous environment of the body (Groff & Gropper 2000).

Iron is found in the body in: haemoglobin (65%); myoglobin (10%); enzymes (1–5%); the transport form, transferrin (0.05%); and the storage forms ferritin (4–9%) and haemosiderin (1–4%).

The haem form of iron is more soluble than the non-haem form and is absorbed 2–3 times more readily. It is absorbed via mucosal cells in the small intestine. Non-haem iron is bound to other substances in food, and must first be liberated by gastric secretions such as hydrochloric acid and pepsin. As such, absorption is best in the acidic environment of the stomach (Groff & Gropper 2000).

Here is a brief summary of the main influences on iron absorption.

Solubility enhancers of non-haem iron

- Acids (including ascorbic acid) aid solubility of non-haem iron, thus improving absorption; the addition of 20 mg ascorbic acid has been shown to increase non-haem iron absorption by 39% (Hallberg et al 2003).
- Sugars (e.g. fructose) aid absorption.
- Meat stimulates digestive secretions, and breakdown products such as cysteine-containing peptides aid absorption (Hurrell et al 1988). The addition of red meat increases non-haem iron absorption by 85% (Hallberg et al 2003). This appears to be dose-dependent, as a recent study found that the addition of 60 g Danish pork meat three times daily improved the absorption of non-haem iron from 5.3% to 7.9% (Bach-Kristensen et al 2005) although the addition of smaller amounts were not as effective (Baech et al 2003).
- The addition of fish to a high-phytate bean meal has also been shown to increase iron absorption (Navas-Carretero et al 2008).
- Alcohol appears to improve iron uptake. The consumption of up to two alcoholic drinks per day is associated with reduced risk of iron deficiency and more than two can increase the risk of iron overload (Ioannou et al 2004).

Solubility inhibitors of non-haem iron

- Polyphenols, including tannin derivatives of gallic acid (tea has been reported to reduce iron absorption by 60%, coffee by 40%) (Kaltwasser et al 1998, Morck et al 1983). A number of studies have shown that tea catechins can inhibit intestinal non-haem iron absorption (Ullmann et al 2005); however, polyphenols do not have chelating effects on cooked haem iron (Breet et al 2005).

> ***Clinical note — Factors affecting the absorption of iron***
> If the dietary intake of iron is adequate, it is often assumed that a patient's iron levels will be within the normal range. In practice, this is not always the case as absorption is significantly affected by a number of factors, thereby increasing or decreasing the amount of ingested dietary iron that reaches the systemic circulation.

Recent studies suggest that impaired absorption is unlikely to be significant in people with normal iron stores (Breet et al 2005, Ullmann et al 2005). The addition of milk to tea may reduce the chelating effects.
- Phytic acid (whole grains).
- Oxalic acid (spinach, chard, chocolate, berries).
- Calcium — single-meal studies have established that calcium (including calcium phosphate and foods such as milk) reduces iron absorption by up to 70% (Hallberg et al 1991); however, the effect may not be as pronounced when calcium is served as part of a whole diet. For instance, the consumption of a glass of milk or the equivalent amount of calcium from fortified food does not appear to decrease non-haem iron absorption (Grinder-Pedersen et al 2004). Although it remains to be shown in iron-deficient persons, long-term iron status does not seem to be compromised by high calcium intake (Molgaard et al 2005).
- Zinc competes with iron for absorption (Solomons 1983) — inorganic zinc supplements may reduce iron absorption by 66–80% (Crofton et al 1989), and supplements containing both iron and zinc may not be as efficacious as the same doses given in isolation (Fischer Walker et al 2005, Lind et al 2003), but nutrients consumed in a meal may not be as affected (Whittaker 1998).
- Manganese may reduce absorption by 22–40% (Rossander-Hulten 1991).
- Rapid intestinal transit time.
- Malabsorption syndromes.
- *Helicobacter pylori* infection (Ciacci et al 2004).
- Gastrointestinal blood loss (Higgins & Rockey 2003).
- Insufficient digestive secretions (including achlorhydria).
- Antacids and proton pump inhibitor drugs.

CHEMICAL COMPONENTS

Ferrous sulfate is the most widely studied form. Other ferrous forms include ascorbate, carbonate, citrate, fumarate, gluconate, lactate, succinate and tartrate (non-haem iron). Iron from ferrous sulfate has a significantly greater bioavailability than ferrous glycine chelate or ferric EDTA (Ferreira da Silva et al 2004). Other ferric forms include ammonium citrate, chloride, citrate, pyrophosphate and sulfate. Amino acid chelates, such as iron glycine, are also available. Dietary ferritin is as equally well absorbed as ferrous sulfate and therefore food sources are likely to be effective (Davila-Hicks et al 2004). Cooking in iron pots may also improve iron status (Geerligs et al 2003).

FOOD SOURCES

The average Western diet is estimated to contain 5–7 mg iron/1000 kcal.

Haem iron

About 50–60% of the iron in animal sources is in the haem form. Sources include liver, lean red meat, poultry, fish, oysters, clams, shellfish, kidney and heart.

Non-haem iron

This is found in plant and dairy products in the form of iron salts and makes up about 85% of the average intake. Sources include nuts, legumes, fruit, dried fruit, vegetables including beetroot, grains and tofu. Dairy is a relatively poor source of iron.

A number of iron-fortified foods are also available and include egg yolks, dried fruit, dark molasses, wholegrain and enriched bread, pasta, cereal, soy sauce, Thai fish sauce, milk, orange juice and wines.

Considering that minerals such as calcium may reduce iron absorption, fortification of some foods may be relatively ineffectual unless absorption enhancers such as vitamin C are also included (Davidsson et al 1998).

DEFICIENCY SIGNS AND SYMPTOMS

Iron deficiency anaemia is considered to be the most common micronutrient deficiency in the world, affecting approximately 1.2 billion people including up to 46% of schoolchildren in developing countries (Sejas et al 2008). Iron deficiency may occur with or without anaemia (Gillespie et al 1991).

Iron deficiency anaemia, also known as hypochromic microcytic anaemia, results in reduced work capacity in adults and a reduced ability to learn in children. Signs and symptoms include:
- fatigue and lethargy
- decreased resistance to infection
- cardiovascular and respiratory changes, which can progress to cardiac failure if left untreated
- increased lead absorption, which in turn inhibits haem synthesis
- decreased selenium and glutathione peroxidase levels
- pale inside lower eyelid or mouth
- pale-coloured nail bed
- pale lines on stretched palm (palmar creases)
- ridged, spoon-shaped, thin flat nails
- brittle hair
- impaired cognitive and motor function
- adverse pregnancy outcomes and increased perinatal maternal mortality (NMCD 2005)
- reduced thyroid function and ability to make thyroid hormones (Beard et al 1990)
- difficulty maintaining body temperature in a cold environment.

Primary deficiency

Primary deficiency is most common in vegetarians, the elderly, those with protein-calorie malnutrition, and during periods of increased iron requirement due to expanded blood volume in infancy, adolescence and pregnancy.

Secondary deficiency

Underlying causes of iron-deficiency anaemia include blood loss, inefficient absorption due to gastrointestinal disturbances and increased destruction of red blood cells.
- Blood loss (menstruation, menorrhagia, bleeding haemorrhoids, parasites, bleeding peptic ulcer, malignancy, *H. pylori* infection, gastrointestinal bleeding due to medication such as NSAIDs).

- Inefficient absorption (chronic gastrointestinal disturbances, malabsorption syndromes, coeliac disease) (Annibale et al 2001).
- Increased destruction of red blood cells (malaria, high-intensity exercise).

Note: The majority of iron utilised in erythropoiesis is provided by recovered iron from old erythrocytes (Handelman & Levin 2008), thus a failure in this system will also impact on iron status.

MAIN ACTIONS

Iron plays a central role in many biochemical processes in the body.

Oxygen transport and storage

The key function of iron is to facilitate oxygen transport by haemoglobin, the oxygen-carrying pigment of erythrocytes. It is also involved in oxygen storage by myoglobin, an iron-containing protein that transports and stores oxygen within muscle and releases it to meet increased metabolic demands during muscle contraction.

Immunity

Iron is vital for the proliferation of all cells including those of the immune system. In vitro and in vivo studies have indicated a link between iron deficiency and impaired T lymphocyte proliferation. In anaemic children in Bolivia who received iron treatment for three months, the proportion of circulating immature T lymphocytes decreased from 18.3% to 9.2% (Sejas et al 2008).

Iron deficiency causes several defects in both humoral and cellular immunity (Bowlus 2003), including a reduction in peripheral T cells secondary to atrophy of the thymus and inhibition of thymocyte proliferation (Bowlus 2003) and a reduction in IL-2 production (Bergman et al 2004). Reduced IL-2 production may partly explain the increased susceptibility to infections and cancer in patients with iron deficiency anaemia (Bergman et al 2004). Supplementation of ferrous sulfate (60 mg Fe) once daily for 8 weeks has been shown to reduce the incidence and duration of upper-respiratory tract infections in children (De-Silva et al 2003).

However, there is also preliminary evidence that iron may be implicated in the pathogenesis of auto-immune disorders, including SLE, scleroderma, type 1 diabetes, Goodpasture syndrome, multiple sclerosis and RA (Bowlus 2003). Current evidence suggests that moderately elevated iron stores may be associated with an overall increased risk for cancer, especially colorectal cancer (McCarty 2003). Additionally, it has been proposed that iron may increase HIV replication and the rate of progression of HIV infection, although doses of 60 mg of elemental iron twice weekly for 4 months did not appear to affect HIV-1 viral load in clinical studies (Olsen et al 2004). Although maintaining adequate iron status may be important for immunity, the benefits of routine supplementation in the absence of deficiency cannot be justified.

Enzyme systems

Both haem and non-haem iron are a part of many enzymes that are involved in:

- cellular respiration
- amino acid metabolism (e.g. carnitine)
- detoxification (as part of cytochrome P450 enzymes in the liver)
- protection against free radical damage
- synthesis of nutrients such as vitamin A
- synthesis of hormones and neurotransmitters (serotonin and noradrenaline)
- synthesis of collagen and elastin.

CLINICAL USE

Iron supplementation is administered using various routes (e.g. by injection or orally). This review will only focus on oral supplementation as this is the form generally used by the public and available OTC.

Iron deficiency

Iron supplementation is used to rectify deficiency states resulting from inadequate intake, increased requirements such as pregnancy, increased losses such as menstruation, and where absorption is affected due to gastric bypass or chronic gastrointestinal disturbances. Currently, researchers are attempting to clarify the best forms, administration routes and dosage regimens to use in different iron deficiency situations.

Iron deficiency anaemia

Previous evidence suggested that weekly administration of iron was an effective strategy for the treatment and prevention of iron deficiency and iron deficiency anaemia in most population groups including pregnant women and children (Agarwal et al 2003, Mukhopadhyay et al 2004, Siddiqui et al 2004, Sungthong et al 2004, Yang et al 2004). Although this is associated with lower cost, fewer side-effects and improved compliance (Haidar et al 2003), this notion has been recently challenged when twice-weekly doses of iron (ferrous dextran containing 60 mg elemental iron) for 12 months failed to improve haemoglobin or serum ferritin (iron stores) in children or adults (Olsen et al 2006). It has since been suggested that weekly doses may assist in maintenance but may not improve iron status (Wijaya-Erhardt et al 2007). Higher doses or

Clinical note — Testing for iron deficiency

In iron deficiency anaemia, storage iron declines until the delivery of iron to bone marrow is insufficient for erythropoiesis to occur. In the early stages, blood tests will reveal low plasma ferritin, followed by decreased plasma iron and transferrin saturation, and ultimately low haemoglobin in red blood cells (Handelman & Levin 2008). As isolated haemoglobin has both low specificity and low sensitivity for determining iron status, the optimal diagnostic approach is to measure the serum ferritin as an index of iron stores and the serum transferrin receptor as an index of tissue iron deficiency (Cook 2005, Flesland et al 2004, Mei et al 2005).

addressing concomitant deficiencies of other micronutrients may be required to obtain the benefits of less frequent dosing regimens.

Children

A recent systematic review revealed that iron supplementation significantly but modestly increased haemoglobin levels in children. The effects appeared to be greater in those who were anaemic at the start of treatment and lower for those in hyper-endemic malarial areas or consuming iron-fortified foods (Gera et al 2007).

In a 2004 study, 60 children (age 5–10 years) with iron deficiency anaemia were given ferrous sulfate (200 mg) daily or weekly for 2 months with similar efficacy and fewer side-effects in the once weekly group (Siddiqui et al 2004). In another study, children receiving weekly doses of ferrous sulfate (300 mg) had similar improvements in haemoglobin, but a significantly higher increase in IQ, compared to those taking the same dose of iron 5 days per week (Sungthong et al 2004). The doses used in these trials may be higher than those actually required to correct deficiency.

Elderly

Patients, such as the elderly, who are particularly vulnerable to the dose-dependent adverse effects of iron supplementation, should be given the lowest effective dose. A randomised trial of 90 hospitalised elderly patients demonstrated that 15 mg of liquid ferrous gluconate produced similar improvements in haemoglobin and ferritin over 60 days to 150 mg of ferrous calcium citrate tablets without the negative side-effects (Rimon et al 2005).

In all cases the lowest safe and effective dose at the lowest frequency of dosing should be used to correct iron deficiency with or without anaemia.

Pregnancy

A recent Cochrane review determined that while severe anaemia can have very serious consequences for mothers and babies, there is a paucity of good quality trials assessing iron supplementation on maternal and neonatal clinical effects. The treatment of mild to moderate anaemia in pregnancy by oral or parenteral (intramuscular and intravenous) administration remains controversial (Reveiz et al 2007). A 2007 study showed that the iron status of children at 6 months and 4 years born to women who were randomly allocated to receive 20 mg of iron daily in the second half of pregnancy did not differ from children of mothers in the control group (Zhou et al 2007a). Another study found that prenatal iron supplementation used to reduce the incidence of iron deficiency anaemia from 11% to 1% had no effect on the IQ of the offspring at 4 years of age (Zhou et al 2006). Due to the possibility of uncontrolled lipid peroxidation, predictive of adverse effects for mother and fetus, iron supplementation should be prescribed on the basis of biological criteria, not on the assumption of anaemia alone (Lachili et al 2001) and the minimum dose possible should be used. Low-dose iron supplements (20 mg elemental iron) have demonstrated efficacy in treating anaemia in pregnancy with less gastrointestinal side effects (Zhou et al 2007b).

According to trials, a supplement of 40 mg ferrous iron/day from 18 weeks gestation appears adequate to prevent iron deficiency in 90% of women and iron deficiency anaemia in at least 95% of women during pregnancy and postpartum (Milman et al 2004). A single weekly dose of 200 mg elemental iron, however, may be sufficient as this has been shown to be comparable with 100 mg elemental iron daily on erythrocyte indices (Mukhopadhyay et al 2004). In recent trials, low doses of sodium feredetate (33 mg and 66 mg of elemental iron given twice daily) produced comparable results to ferrous fumarate (100 mg elemental iron given twice daily) with no reports of adverse effects; however, larger scale trials are required to confirm these effects (Sarkate et al 2007).

Although iron supplementation is often used as stand-alone treatment in pregnant iron-deficient women, one RCT indicated that a combination of iron and folate therapy (80 mg iron protein succinylate, with 0.370 mg folinic acid daily) for 60 days produces a better therapeutic response than iron-only supplementation (Juarez-Vazquez et al 2002).

Postpartum anaemia

Postpartum anaemia is associated with breathlessness, tiredness, palpitations, maternal infections and impaired mood and cognition. A 2004 Cochrane review suggested that further high-quality trials were required before the benefits of iron supplementation or iron-rich diets in the treatment of postpartum anaemia could be established (Dodd et al 2004). Since then a randomised placebo-controlled study of iron sulfate (80 mg daily) for 12 weeks starting 24–48 hours after delivery demonstrated an improvement in haemoglobin levels and iron stores (Krafft et al 2005) and supplementation of ferrous sulfate (125 mg) with folate (10 μg) and vitamin C (25 mg) demonstrated improvements in cognitive function, as well as depression and stress compared with folate and vitamin C alone (Beard et al 2005). However, further studies are still warranted.

Unexplained fatigue without anaemia

Iron supplementation is sometimes used in women who are not anaemic (haemoglobin >117 g/L) yet complain of fatigue. A recent, double-blind, randomised placebo-controlled trial designed to determine the subjective response to iron therapy in non-anaemic women (haemoglobin >117 g/L) with unexplained fatigue found that supplementation with oral ferrous sulfate (80 mg/day elemental iron) for 4 weeks reduced the level of fatigue in the iron group by 29% compared with 13% in the placebo group. Subgroup analysis showed that only women with ferritin concentrations <50 μg/L improved with oral supplementation. This was common in 85% of subjects and 51% of subjects had ferritin concentrations <20 μg/L (Verdon et al 2003). This study suggests that iron deficiency anaemia may be present despite haemoglobin and

ferritin levels being within the 'normal' range and that the lower reference levels for women may need to be revised.

Improving athletic performance in marginally deficient people

Sports anaemia is a common finding among professional and non-professional athletes engaging in strenuous physical activity. Possible mechanisms include: dilutional pseudoanaemia, which is caused by plasma volume expansion greater than that of the red blood cell mass, but does not reflect actual blood loss and will generally normalise within 3–5 days of ceasing training; intravascular haemolysis due to mechanical trauma such as 'foot strike haemolysis', which can result in urinary loss of iron; or transient ischaemia resulting from vasoconstriction of the splanchnic and renal vessels, which can also result in blood loss from the gastrointestinal and urinary tracts (Merkel et al 2005).

In a placebo-controlled trial, iron supplementation (50 mg ferrous sulfate twice daily) for 6 weeks significantly improved iron status and maximal oxygen uptake ($\dot{V}O_{2max}$) after 4 weeks' concurrent aerobic training in previously marginally deficient and untrained women (Brownlie et al 2002). In a later randomised double-blind placebo-controlled study of 41 untrained iron-deficient women without anaemia, ferrous sulfate (100 mg) for 6 weeks improved endurance capacity after aerobic training (Brownlie et al 2004). However, a recent review concluded that the current evidence does not justify the use of supplementation solely for the purpose of performance enhancement (Rodenberg & Gustafson 2007).

Due to the potential side-effects of inappropriate iron supplementation and the possibility of masking more serious underlying complaints, athletes should only be supplemented if iron deficiency is established on the basis of biological criteria (Zoller & Vogel 2004). Supplementing antioxidants (vitamin E 500 mg/day, vitamin C 1 g/day, beta-carotene 30 mg/day) may assist in preventing exercise-induced decreases in iron status and antioxidant defences (Aguilo et al 2004) and may be a safer option in iron-replete athletes.

Anaemia of inflammation/chronic disease

In this form of anaemia storage iron is often abundant but not available for erythropoiesis. Thus, elevated markers of inflammation should be used for diagnosis. Treatment is difficult but often involves intravenous iron and erythropoietin (EPO) supplements (Handelman & Levin 2008).

Perioperative care

Iron is sometimes given before surgery to reduce postoperative decreases in haemoglobin (Andrews et al 1997). However, this use is contentious and numerous studies have failed to report benefits for preoperative autologous blood collection (Cid et al 2005) or for correcting anaemia associated with cardiac surgery (Madi-Jebara et al 2004) or orthopaedic surgery, such as hip or knee arthroplasty (Mundy et al 2005, Weatherall & Maling 2004). In a more recent randomised placebo-controlled trial in patients undergoing colorectal surgery, oral ferrous sulfate (200 mg TDS) for 2 weeks pre-operatively resulted in increased mean haemoglobin and ferritin concentrations, and reduced the need for operative blood transfusion (mean 0 units transfused [range, 0–4 units] versus 2 units transfused [range, 0–11 units]; $P = 0.031$; 95% CI 0.13–2.59) (Lidder et al 2007).

Gastric bypass patients

Iron deficiency may develop after gastric bypass due to red meat intolerance, diminished gastric acid secretion and exclusion of the duodenum from the gastrointestinal tract. Patients require lifelong follow-up of hematological and iron parameters since iron deficiency and anaemia may develop years after surgery and, once developed, may prove refractory to oral treatment, resulting in the need for parenteral iron, blood transfusions or surgical interventions (Love & Billett 2008).

Cognitive function

Iron supplementation has been shown to improve cognitive function and depression in postpartum anaemic women (Beard et al 2005); however, the majority of trials in this area focus on childhood development. An association between iron-deficiency anaemia and poor cognitive and motor development with behavioural problems has been observed, and attention deficit may be substantially improved with iron supplementation (elemental iron 5 mg/kg/day) for up to 3 months (Otero et al 2004). Two-month supplementation of 15 mg iron (and multivitamin) versus multivitamin alone in preschoolers with iron-deficiency anaemia resulted in improvements in discrimination (specifically selective attention), accuracy and efficiency (Metallinos-Katsaras et al 2004).

Recently however, a systematic review reported no effects on motor development scores and only modest improvements in mental development scores, although these were more prevalent in those who were initially anaemic or iron deficient (Sachdev et al 2005). Preventing iron deficiency appears to be a rapid and effective means of improving infant lead levels, even in non-anaemic infants (Wolf et al 2003) and this may also contribute to benefits in some children.

Improving cognition in children and postpartum women appears to be the result of correcting iron deficiency and it cannot be inferred that iron supplementation will benefit cognitive function in iron-replete individuals.

Attention deficit hyperactivity disorder (ADHD) in children

Preliminary evidence suggests that iron deficiency might contribute to ADHD (as well as restless leg syndrome and Tourette's) via its impact on the metabolism of dopamine and other catecholamines (Cortese et al 2008). As a result, children with ADHD and a positive family history of restless leg syndrome appear to be at increased risk for severe ADHD symptoms (Konofal et al 2007). Iron

supplementation (80 mg/day) for 12 weeks appeared to significantly improve ADHD symptoms in children with low serum ferritin levels but without anaemia. The mean Clinical Global Impression-Severity ($P < 0.01$) and ADHD Rating Scale (–11.0 ± 13.9; $P < 0.008$) were improved in a manner comparable to stimulants (Konofal et al 2008).

Blood donors

Iron supplementation (150 mg ferrous sulfate TDS) for 1 week following blood donation reduced the decline in haemoglobin concentration and maintained haematocrit, serum iron, serum ferritin and percent saturation (Maghsudlu et al 2008). Normalisation of low haemoglobin, and thus blood donor retention, may be further enhanced by a standardised protocol offering iron supplementation and simple oral and written advice based on plasma ferritin measurements (Magnussen et al 2008).

OTHER USES

Breath-holding spells

Iron supplementation may significantly reduce the incidence of breath holding spells, especially in iron-deficient children as shown in an RCT (Daoud et al 1997).

Haemodialysis

Intravenous iron is frequently, but contentiously, prescribed for the aggressive management of anaemia associated with dialysis (Agarwal et al 2004, Gillespie & Wolf 2004, Ruiz-Jaramillo et al 2004). CYP3A4 activity is reduced in haemodialysis patients, which may be related to functional iron deficiency. However, with the exception of a subset of haemodialysis patients with low baseline CYP3A4 activity, IV iron does not appear to have a significant effect on hepatic CYP3A4 (Pai et al 2007). It has been suggested that strategies to improve vitamin C status and to decrease inflammation would lead to better utilisation of iron in these patients (Handelman 2007).

DOSAGE RANGE

- Therapeutic dose: 2–5 mg/kg/day; however, in many cases the equivalent of this dose may be given weekly.
- In cases of deficiency, initial effects on haemoglobin and erythrocyte concentrations take about 2 weeks but it may take 6–12 months to build iron stores (Groff & Gropper 2000).
- The Australian Iron Status Advisory Panel advocates dietary intervention as the first treatment option for mild iron deficiency (serum ferritin 10–15 μg/L) (Patterson et al 2001). Trials have shown a significant increase in serum ferritin levels (26%) using dietary intervention alone (Heath et al 2001).

In Table 1, the RDI of iron is expressed as a range to allow for differences in bioavailability of iron from different Australian foods.

Studies have shown that there can be a significant sex difference in haemoglobin and other indicators of iron status during infancy. Some of these may be genetically determined, whereas others seem to reflect an increased incidence of true iron deficiency in boys (Domellof et al 2002).

TOXICITY

Iron toxicity causes severe organ damage and death. The most pronounced effects are haemorrhagic necrosis of the gastrointestinal tract, which manifests as vomiting, bloody diarrhoea and hepatotoxicity.

Conditions that increase risk of toxicity include:

- Haemochromatosis (iron overload) — excess storage of iron in the body, which can cause organ and tissue damage (especially liver and heart) and an increased risk for hepatic carcinoma. It may be caused by an excessive oral intake, a genetic defect that causes the body to absorb more iron than normal, or repeated blood transfusions.
- Haemosiderosis — iron overload without tissue damage.
- Iron-loading anaemias — thalassaemia and sidero blastic anaemia.

ADVERSE REACTIONS

Oral supplements may cause gastrointestinal disturbances such as nausea, diarrhoea, constipation, heartburn and upper gastric discomfort.

Taking supplements with food appears to reduce the possibility of gastrointestinal side-effects. Liquid iron preparations can discolour teeth — brush teeth after use.

In the absence of appropriate storage or chelation, excess free-iron can readily participate in the formation of toxic free-radicals, inducing oxidative stress and apoptosis (Whitnall & Richardson 2006). Iron depletion leads to decreased availability of redox-active iron in vivo and appears to reduce atherosclerotic lesion size and increase plaque stability (Sullivan & Mascitelli 2007). Iron toxicity and subsequent organ damage can develop from long-term excessive intake.

There is preliminary evidence that iron may be implicated in the pathogenesis of auto-immune disorders (Bowlus 2003) and neurodegenerative diseases (Whitnall & Richardson 2006); and that moderately elevated iron stores may be associated with an overall increased risk for cancer, especially

TABLE 1 Australian Recommended Daily Intake by age and sex

Age	Australian RDI (mg/day)
Infants (0–6 months; breastfed)	0.2
Infants (7–12 months)	11
Children (1–13 years)	8–10
Girls (14–18 years)	15
Boys (14–18 years)	11
Men (>19 years)	8
Women (19 to menopause)	18
After menopause	8
Pregnancy	27
Lactation	9

TABLE 2 Summary of Iron Interactions

Drug/ therapeutic substance	Mechanism	Possible outcome	Action required
ACE inhibitors	Reduced absorption of ACE inhibitors. A small clinical trial found that concomitant iron administration reduced area-under-the-curve plasma levels of unconjugated captopril by 37% (Lee et al 2001, Schaefer et al 1998).	Reduced drug effect	Separate doses by at least 2 hours.
Antacids and products containing aluminium, calcium or magnesium	Reduces iron absorption (O'Neil-Cutting & Crosby 1986).	Reduced effect of iron	Separate doses by at least 2 hours.
Ascorbic acid	Increases iron absorption.	Increased effects of iron	Beneficial interaction is possible — caution in haemochromatosis.
Cholestyramine and colestipol	In vitro investigations have shown that cholestyramine and colestipol both bind iron citrate (Leonard et al 1979).	Reduced drug and iron effect	Monitor for iron efficacy if cholestyramine is being used concurrently. Separate doses by 4 hours. Increased iron intake may be required with long-term therapy.
Cimetidine	Iron can bind cimetidine in the gastrointestinal tract and reduce its absorption (Campbell et al 1993).	Reduced drug and iron effect	Separate doses by at least 2 hours.
Dairy products and eggs	May reduce iron absorption.	Reduced effect of iron	Monitor for iron efficacy.
Erythropoietin	Pharmacodynamic interaction (Carnielli et al 1998). In patients with chemotherapy-related anaemia without iron deficiency, the addition of IV iron supplementation may improve the success of darbepoetin (92.5% versus 70% for darbepoetin alone; $P = 0.0033$) without increasing toxicity (Pedrazzoli et al 2008).	Additive pharmaco-logical effect possible	Beneficial interaction is possible.
H_2-receptor antagonists (antiulcer drugs)	Iron absorption is dependent upon gastric pH; therefore, medications that affect gastric pH may interfere with absorption of iron (Aymard et al 1988).	Reduced effect of iron	Monitor for iron efficacy if these drugs are being used concurrently.
Haloperidol	May cause decreased blood levels of iron (Leenders et al 1994, Threlkeld 1998).	Reduced effect of iron	Monitor for iron efficacy if these drugs are being used concurrently. Increased iron intake may be required with long-term therapy.
L-Dopa and carbidopa	May reduce bioavailability of carbidopa and L-dopa (van Woert 1977).	Reduced drug effect	Separate doses by 2 hours.
Omeprazole and other proton-pump inhibitors	Reduced iron absorption due to changes in gastric pH	Reduced effect of iron	Monitor for iron efficacy if omeprazole is being used concurrently.

TABLE 2 Summary of Iron Interactions (*continued*)

Drug/ therapeutic substance	Mechanism	Possible outcome	Action required
Penicillamine	Reduced drug and iron absorption	Reduced drug and iron effect	Separate doses by at least 2 hours. Sudden withdrawal of iron during penicillamine use has been associated with penicillamine toxicity and kidney damage (Harkness & Blake 1982) — caution.
Quinolone antibiotics (e.g. norfloxacin)	Reduced drug absorption (Brouwers 1992)	Reduced drug effect	Take drug 2 hours before or 4–6 hours after iron dosing. Monitor patient for continued antibiotic efficacy.
Sulfasalazine	May bind together, decreasing the absorption of both (Dukes & Duncan 1995).	Reduced drug and iron effect	Separate doses by at least 2 hours.
Tannins — herbs with significant tannin content (e.g. green tea, bilberry, raspberry leaf)	Tannin can bind to iron and reduce its absorption.	Reduced effect of iron	Monitor for iron efficacy if these herbs are being used concurrently. Separate doses by 2 hours.
Tetracycline antibiotics (e.g. minocycline, doxycycline)	While early studies suggested reduced drug and iron absorption (Neuvonen 1976), recent human data found no effect on erythrocyte iron uptake when in patients taking 100 mg iron orally and oral tetracycline (Potgieter et al 2007).	Reduced drug effect	Monitor for iron efficacy if tetracyclines are being used long term. Separate doses by 4 hours.
L-Thyroxine	Decreased drug absorption possible. Iron supplements may decrease absorption of thyroid medication; however, iron deficiency may impair the body's ability to make thyroid hormones.	Reduced drug effect	Thyroid function should be monitored and L-thyroxine dose may need alteration during treatment with iron. Separate doses by at least 2–4 hours (Shakir et al 1997).
Vitamin A	Iron supplementation may cause a redistribution of retinol inducing vitamin A deficiency in infants with marginal vitamin A status (Wieringa et al 2003).	Redistribution of retinol	Iron supplementation in infants should be accompanied by measures to improve vitamin A status.

colorectal cancer (McCarty 2003). In younger people iron depletion is associated with a reduced risk of all-cause mortality (Sullivan & Mascitelli 2007), although numerous confounding factors cannot be ignored. While haem-iron intake from red meat may present a risk for increased blood pressure, non-haem dietary intake may slightly reduce systolic blood pressure (Tzoulaki et al 2008). For the time being, supplementation without demonstrated biological need cannot be justified as the potential risks may outweigh any short-term benefits.

SIGNIFICANT INTERACTIONS

Iron interacts with a variety of foods, herbs and drugs through several different mechanisms. Most commonly, the formation of insoluble complexes occurs whereby both iron and drug absorption is hindered. Separation of doses by several hours will often reduce the severity of this type of interaction. Additionally, substances that alter gastric pH have the theoretical ability to reduce iron absorption. A summary of interactions is presented in Table 2 for easy reference.

CONTRAINDICATIONS AND PRECAUTIONS

Iron poisoning can occur due to accidental ingestion of excess iron supplements. As such, iron supplements should be kept in childproof bottles and out of the reach of children.

Caution should be exercised when supplementing iron to infants or children with apparently normal growth when the iron status of the child is unknown. A double-blind placebo-controlled trial showed that while iron therapy produced a significant improvement of mean monthly weight gain and linear growth in iron-deficient children, it significantly decreased the weight gain and linear growth of iron-replete children (Majumdar et al 2003). This study confirms the results of earlier studies (Dewey et al 2002).

- Iron supplements should not be used in haemochromatosis, haemosiderosis, or iron-loading anaemias (thalassaemia, sideroblastic anaemia).
- Daily oral iron supplementation providing 50 mg elemental iron for 8 weeks did not result in increased oxidative damage in the plasma of college-aged women (Gropper et al 2003). However, more recently 100 mg doses of iron daily for 8 weeks were shown to increase lipid peroxidation. As iron status and duration of supplementation increased so too did indicators of lipid peroxidation (King et al 2008). As the use of iron supplements may potentially result in oxidative damage, risk should always be assessed against benefit before prescribing iron supplements.
- Elevated levels of serum ferritin have been implicated in the pathogenesis of vascular (and other) diseases, although this remains controversial (McCarty 2003, Zacharski et al 2004).

PRACTICE POINTS/PATIENT COUNSELLING

- Iron is an essential mineral that facilitates oxygen transport and storage in the body and is part of many enzyme systems.
- Haem iron, found in animal products, is absorbed 2–3-fold better than non-haem forms found in vegetable sources. However, iron absorption is influenced by many factors, such as other foods ingested, medicines and gastric activity.
- Iron deficiency is the most common nutritional deficiency in the world and may occur with or without anaemia. Excessive blood loss during menstruation is the most common cause.
- Supplements are generally used to treat or prevent deficiency. Excess iron can be dangerous and can lead to organ damage and death.
- As inappropriate iron supplementation can inhibit growth in non-deficient children and adversely affect pregnancy outcomes, iron status should be tested before administration.
- Correction of iron deficiency with or without anaemia may be achieved with lower doses than those recommended in some trials. In many cases, once weekly dosing of iron is as effective as daily dosing and improves compliance while reducing side-effects and cost.
- Haem-rich flesh foods may need to be limited in people with insulin resistance due to a possible link with increased cancer risk mediated by iron excess in such populations (McCarty 2003).
- Iron supplementation should be prescribed on the basis of biological criteria, not on the assumption of anaemia alone, as unnecessary iron supplementation can result in adverse effects. The lowest safe and effective dose and frequency of dose should be recommended.

PREGNANCY USE

Oral iron preparations are considered safe in pregnancy; however, unnecessary iron supplementation can result in uncontrolled lipid peroxidation (Lachili et al 2001), lowered serum levels of copper and zinc (Ziaei et al 2008), low birth weight and maternal hypertension disorder (Ziaei et al 2007). Routine iron supplementation in non-anaemic women is not justified and may be harmful, so supplementation should be prescribed on the basis of biological criteria, not on the assumption of anaemia alone.

PATIENTS' FAQs

What will this supplement do for me?

Iron is necessary for health and wellbeing. It facilitates oxygen transport and storage in the body and is part of many enzyme systems. Iron deficiency is the most common deficiency in the world.

When will it start to work?

Iron deficiency responds to supplementation within 2 weeks; however, 6–12 months may be required to build up the body's iron stores.

Are there any safety issues?

Excess iron can be dangerous and ultimately can lead to severe organ damage and death.

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Kava kava

HISTORICAL NOTE For many centuries, Pacific Islanders have used the kava kava root to prepare a beverage used in welcoming ceremonies for important visitors. Drinking kava kava is not only done to induce pleasant mental states but also to reduce anxiety and promote socialising. It is believed that the first report about kava kava came to the West from Captain James Cook during his voyages through the Pacific region.

COMMON NAME
Kava kava

OTHER NAMES
Kawa, awa, intoxicating pepper, rauschpfeffer, sakau, tonga, yagona

BOTANICAL NAME/FAMILY
Piper methysticum (family Piperaceae)

PLANT PARTS USED
Root and rhizome

CHEMICAL COMPONENTS
The most important constituents responsible for the pharmacological activity of kava rhizome are the fat-soluble kava lactones (kavapyrones), mainly methysticin, dihydromethisticin, kavain, dihydrokavain and desmethoxyangonin and flavonoids (flavokavains).

MAIN ACTIONS

Central nervous system (CNS) effects
The kava lactones reach a large number of targets that influence CNS activity and act centrally and peripherally. They interact with dopaminergic, serotonergic, GABA-ergic and glutamatergic neurotransmission, seem to inhibit monoamine oxidase B and exert multiple effects on ion channels, according to in vitro and in vivo research (Grunze et al 2001). Additionally, animal studies show that kava lactones are chiefly responsible for these effects that give rise to many of the herb's clinical actions (Cairney et al 2002).

Hypnotic
Although the exact mechanism of action is not yet understood, it has been observed that sleep promotion may be due to the preferential activity of D,L-kavain and kava kava extract on the limbic structures and, in particular, the amygdalar complex (Holm et al 1991) in the brain.

In an electroencephalogram (EEG) brain-mapping study it was demonstrated that D,L-kavain could induce a dose-dependent increase in delta-, theta- and alpha-1 power, as well as a decrease in alpha-2 and beta power. These results indicate a sedative effect at the higher dose range (Frey 1991).

Anxiolytic effects
A recent study showed that kava kava extract produces a statistically significant dose-dependent anxiolytic-like behavioural change in rat models of anxiety (Garrett et al 2003). The effect is not mediated through the benzodiazepine binding site on the GABA-A receptor complex, as flumazenil, a competitive benzodiazepine receptor antagonist, did not block this effect. Meta-analyses confirm that the anxiolytic effect is clinically significant and comparable to benzodiazepines.

Analgesic and local anaesthetic
Both the aqueous and lipid-soluble extracts of kava kava exhibit antinociceptive properties in experimental animal models (Jamieson & Duffield 1990). The effect is not mediated by an opiate pathway, as naloxone does not reduce the effects when administered in doses that reverse the effects of morphine. More recently, in vitro research has identified several compounds found in kava kava that have the ability to inhibit COX-1 and to a lesser extent COX-2 enzyme activities (Wu et al 2002).

The local anaesthetic effect of kava kava is well known for topical use and has been described as similar to procaine and cocaine (Mills & Bone 2000).

Antispasmodic activity
Antispasmodic activity for skeletal muscle has been observed in vitro and in vivo for both kava kava extract and kava lactones (Mills & Bone 2000). In vivo research suggests that kavain impairs vascular smooth muscle contraction, likely through inhibition of calcium channels (Martin et al 2002).

OTHER ACTIONS

Cytochrome inhibition
In vitro studies published in 2002 suggested that whole kava kava extract and kava lactones have widespread inhibitory effects on various cytochrome enzymes,

such as CYP3A4 (Unger et al 2002), whereas in vivo tests found no effects on CYP3A4/5, CYP1A2 or CYP2D6, but did demonstrate significant inhibition (approximately 40%) of CYP2E1 (Gurley et al 2005). Clinical tests confirm no significant effect on CYP2D6 (Gurley et al 2008).

Animal studies found that kava kava extract decreased the expression of CYP2D1 (human CYP2D6 homolog) at a dose of 2.0 g/kg in females and increased the expression of CYP1A2, 2B1 and 3A1 in 1.0 and 2.0 g/kg groups of both sexes (Clayton et al 2007). The clinical relevance of these findings is unclear, as the doses used were extremely large and not clinically relevant.

CLINICAL USE

Kava kava extracts are popular in Europe and have been investigated in numerous clinical trials, primarily in European countries. As a result, many research papers have been published in languages other than English. In order to provide a more complete description of the evidence available, secondary sources have been used where necessary. The extract which has been most studied is kava kava extract WS®1490.

Anxiety

Evidence from double-blind clinical studies indicates that kava kava is an effective treatment for anxiety, repeatedly shown to be as effective as benzodiazepines.

A 2000 Cochrane review of the scientific literature assessed the results from seven, double-blind, randomised, placebo-controlled trials and concluded that kava kava extract has significant anxiolytic activity and is superior to placebo for the symptomatic treatment of anxiety (Pittler & Ernst 2000). An update of this review was published in 2003 and analysed results from 12 clinical studies involving 700 subjects (Pittler & Ernst 2003). The results of seven studies that used the Hamilton Anxiety Scale (HAM-A) score were pooled and a significant reduction in anxiety was observed for kava kava treatment compared with placebo. The results of the five studies that were not submitted to meta-analysis largely support these findings. The extract most commonly tested was WS 1490 at a dose of up to 300 mg daily.

According to the authors of the review, none of the trials reported any hepatotoxic events and seven trials measured liver enzyme levels as safety parameters and reported no clinically significant changes.

In 2005, Witte et al published results of another meta-analysis which included data from six placebo-controlled, randomised trials with the kava kava extract WS®1490. The endpoints were the change in HAMA during treatment (continuous and binary). Kava kava significantly improved anxiety with a mean improvement of 5.94 points on the HAMA scale better than placebo. Interestingly, kava kava seemed to be more effective in females and in younger patients. The rigorous meta-analysis found no evidence of publication bias, no remarkable heterogeneity amongst the studies and concluded that trials had high methodological standards. Based on this impressive result, authors concluded that kava kava remains as an effective alternative to benzodiazepines, selective serotonin re-uptake inhibitors (SSRIs) and other antidepressants in the treatment of non-psychotic anxiety disorders.

Generalised anxiety disorder

An 8-week randomised, double-blind, multicentre clinical trial involving 129 outpatients with GAD showed that kava kava LI 150 (400 mg/day) was as effective as buspirone in the acute treatment of GAD, with about 75% of patients responding to treatment (Boerner et al 2003).

Comparative studies

Comparative studies suggest the absence of significant differences between benzodiazepines and kavain or kava kava extract as treatments for anxiety. A 1993 double-blind, comparative study involving 174 subjects over 6 weeks demonstrated that 300 mg/day of a 70% kava lactone extract produced a similar improvement in anxiety level, as measured by HAM-A scores, to 15 mg oxazepam or 9 mg bromazepam taken daily (Woelk et al 1993). D,L-kavain produced equivalent anxiolytic effects to oxazepam in 38 outpatients with neurotic or psychosomatic disturbances, under double-blind study conditions (Lindenberg & Pitule-Schodel 1990).

Benzodiazepine withdrawal

Kava kava may have a role in reducing anxiety and improving subjective wellbeing during benzodiazepine withdrawal, according to a 2001 randomised, double-blind, placebo-controlled study (Malsch & Kieser 2001). During the first 2 weeks of that study, kava kava dose was increased from 50 mg/day to 300 mg/day while benzodiazepine use was tapered off during the same period. Kava kava extract was superior to placebo in reducing anxiety as measured by the HAM-A scale and improved subjects' feelings of wellbeing according to a subjective wellbeing scale (Bf-S total scores).

Lack of tolerance

The results from a randomised, double-blind trial conducted over 25 weeks have found that physical tolerance does not develop to kava kava extract and it is well tolerated (Volz & Kieser 1997). Evidence from a randomised, double-blind study conducted with 84 patients has shown that treatment with kavain (one of the active constituents of kava kava) produces continuous improvements in parameters such as memory function, vigilance, fluency of mental functions and reaction time. Interestingly, these effects were reported over a relatively short period of 3 weeks (Scholing & Clausen 1977). Another randomised, double-blind trial conducted with 52 patients over 28 days not only confirmed anxiolytic activity but also found that kavain promoted subjective vitality-related performance (Lehmann et al 1989).

Commission E approves the use of kava kava in conditions of nervous anxiety and restlessness (Blumenthal et al 2000).

Menopausal and perimenopausal anxiety

A randomised, placebo-controlled study conducted with 40 menopausal women found that using kava kava extract, together with hormone replacement therapy (HRT), led to significant reductions in anxiety, as measured by the HAM-A scale at both 3- and 6-month follow-up (De et al 2000). A 3-month, randomised, open study of 68 perimenopausal women showed that treatment with kava kava (100 mg/day) significantly reduced anxiety ($P < 0.001$) at 1 month and 3 months. This was significantly greater than that spontaneously occurring in controls ($P < 0.009$) (Cagnacci et al 2003).

Insomnia

The hypnotic activity of kava kava extract was confirmed in a RCT in which a single dose of 300 mg kava kava extract was found to improve the quality of sleep significantly (Emser & Bartylla 1991, as reported by Ernst et al 2001). In vivo experiments with D,L-kavain have shown that it reduces active wakefulness and significantly prolongs sleep, compared with placebo (Holm et al 1991).

OTHER USES

Traditionally, the herb has been used to treat urinary tract infections, asthma, conditions associated with pain, gonorrhoea and syphilis, and to assist with weight reduction, muscle relaxation and sleep. Topically, it has been used as a local anaesthetic and to treat pruritus.

DOSAGE RANGE

- Cut rhizome: 1.7–3.4 g/day.
- Dried rhizome: 1.5–3 g/day in divided doses or equivalent to 60–120 mg kavapyrones daily.
- Fluid extract (1:2): 3–8.5 mL/day in divided doses.
- Ideally, ethanolic extracts should contain > 20 mg/mL kava lactones.

According to clinical studies

- Anxiety: generally doses up to 300 mg daily of kava kava extract WS 1490 providing 105–210 mg kavalactones. A kava kava extract LI 150 (400 mg/day) was used successfully in generalised anxiety disorder.
- Insomnia — a single dose of 300 mg kava kava extract.
- Benzodiazepine withdrawal — 300 mg/day of kava kava extract.

ADVERSE REACTIONS

In RCT, the incidence of adverse effects to kava kava has been found to be similar to placebo. Two postmarketing surveillance studies involving more than 6000 patients found adverse effects in 2.3% and 1.5% of patients taking 120–240 mg standardised extract (Ernst 2002). The most common side effects appear to be gastrointestinal upset and headaches when used in recommended doses.

Hepatotoxicity

A systematic review assessing the safety of kava kava which included a total of 7078 patients taking kava kava extract equivalent to 10 mg to 240 mg kava lactones per day for 5–7 weeks identified no cases of hepatotoxicity (Stevinson et al 2002). Considering that case reports of hepatotoxicity exist, they should be considered a very rare event based on the evidence.

In 2008, a quantitative causality assessment of 26 critical cases came to a similar conclusion stating kava kava taken as recommended is associated with rare hepatotoxicity, whereas overdose, prolonged treatment, and co-medication may carry an increased risk (Teschke et al 2008). Importantly, a recent World Health Organization report identified that liver toxicity risk is associated with kava kava acetonic and ethanolic extracts, whereas the traditional kava kava preparation which has been prepared for centuries in water does not have the same risk of liver injury.

To put the risk into perspective, estimates from case reports and the sales figures of kava kava extracts (using data from Germany) show an incidence rate of one potential case in 60–125 million patients for liver toxicity (Sorrentino et al 2006).

Possible mechanisms for kava-kava-induced hepatotoxicity

The exact cause remains elusive; however, several mechanisms have been proposed. Genetic polymorphism of cytochrome enzymes, leading to interindividual variation in drug metabolism, may be one important factor in the marked discrepancy in hepatotoxic response to kava kava (Singh 2005). Other possible mechanisms are inhibition of cytochrome P450 by kava kava, reduction in liver glutathione content and, more remotely, inhibition of cyclooxygenase enzyme activity. The direct toxicity of kava kava extracts is quite small under any analysis; yet, the potential for drug interactions and/or the potentiation of the toxicity of other compounds is larger (Clouatre 2004). Recent animal tests with three different kava kava extracts (a methanolic and an acetonic root and a methanolic leaf extract) indicate that the these kava kava extracts are toxic to mitochondria, leading to inhibition of the respiratory chain, increased reactive oxygen species (ROS) production, a decrease in the mitochondrial membrane potential and eventually to apoptosis of exposed cells. In predisposed patients, mitochondrial toxicity of kava kava extract may provide another explanation for hepatotoxic reactions (Lude et al 2008). It has also been suggested that reactions are immunologically mediated (Schulze et al 2003). Considering that the toxic reactions are limited to methanolic and ethanolic extracts, it is possible that chemicals other than kava lactones, such as alkaloids not bioavailable in water extracts, may be responsible for hepatotoxicity.

Long-term use

Heavy kava kava drinkers acquire a reversible ichthyosiform eruption, known as kanikani in Fijian or 'kava dermopathy' in English-speaking countries. This condition is characterised by yellow discolouration of the skin, hair and nails. This temporary condition reverses once kava kava use is discontinued. A 2003 report found no evidence of brain dysfunction in heavy and long-term kava kava users (Cairney et al 2003).

Clinical note — Commercial kava kava products and links to hepatotoxicity

Conflicting reports abound. On 15 August 2002, the Therapeutic Goods Administration (TGA) initiated a voluntary recall of all products containing kava kava. The response was undertaken due to incoming details from European countries of case reports of hepatotoxicity apparently associated with the use of commercial kava kava products.

The decision to remove kava kava from the market has been viewed as controversial and questioned by many people. Toxicological and clinical studies have shown that kava kava extracts are virtually devoid of toxic effects and, when assessed primarily by the British regulatory authority (MCA) and a German research group, a critical analysis of the suspected cases in Germany reveals that a very probable causal relationship could be established in only one patient (Teschke et al 2003). It is suspected that a rare, immunologically mediated, idiosyncratic mechanism may be responsible (Schulze et al 2003) and the extraction process used to produce kava kava products also had an influence. It now appears that the aqueous method results in extraction of glutathione, in addition to kava lactones, an important factor for protecting the liver from potential damage, whereas the acetone extraction method does not (Whitton et al 2003). As a result, kava kava products made with the acetone extraction process are more toxic than those produced via aqueous extraction methods. This is an important distinction to make, as most European products were made using acetone extraction, whereas Australian products were chiefly made via aqueous extraction.

Interestingly, fulminant hepatic failure has not been documented with traditional use either in Pacific countries or in the Northern Territory, where Aboriginal kava kava drinkers consume kava lactones in doses estimated to be 10–50-fold the recommended levels (Currie & Clough 2003). Several reports published in 2003 have found no evidence of aqueous kava kava extracts inducing irreversible liver toxicity in vivo (Singh & Devkota 2003) or in humans (Clough et al 2003). One study involving long-term users of aqueous kava kava extracts found that although changes to liver function could occur at moderate levels of consumption, they are reversible and begin to return to baseline after 1–2 weeks' abstinence from kava kava. A recent animal study testing large concentrations of kava lactones (7.3 or 73 mg/kg of kava lactones/day) over 3 months and 6 months found no signs of toxicity. In addition, no behavioural or physiological changes were observed on discontinuation of kava lactone feeding after 3 months (Sorrentino et al 2006).

Australia was not alone, and other countries also issued health advisory cautions or banned kava kava-containing products from sale. Although these actions effectively removed kava kava products from the market, the traditional kava kava beverage continued to be consumed in the Pacific Islands and the kava kava-producing countries of the Pacific found the controversy surprising, given the long history of apparent safe use in the Pacific. The impact of European and UK withdrawal of kava kava was devastating to the South Pacific economies. In January 2003, the Kava Evaluation Group was established in Australia to review the accumulating safety data and by August that same year the Complementary Medicine Evaluation Committee recommended to the TGA that certain forms of kava kava could be considered safe. The TGA accepted these recommendations and amended the regulations accordingly. Currently in Australia, there is a maximum limit of 125 mg kava lactones allowable per tablet or capsule, 3 g of dried rhizome per tea bag and all products containing kava kava must not provide more than 250 mg kava lactones in the recommended daily dose.

The World Health Organization published a report in May 2007 entitled *Assessment of the risk of hepatotoxicity with kava products* (WHO 2007). It evaluated data from 93 case reports of which 8 were determined to have a close association between the use of kava kava and liver dysfunction; 53 cases were classified as having a possible relationship, but they could not be fully assessed due to insufficient data or other potential causes of liver damage; 5 cases had a positive rechallenge. Most of the other case reports could not be evaluated due to lack of information. It concluded that there is 'significant concern' for a cause and effect relationship between kava kava products and hepatotoxity, especially for organic extracts. Other risk factors appear to include heavy alcohol intake, preexisting liver disease, genetic polymorphisms of cytochrome P450 enzymes, excessive dosage and co-medication with other potentially hepatotoxic drugs and potentially interacting drugs.

SIGNIFICANT INTERACTIONS

Alcohol

Potentiation of CNS sedative effects has been reported in an animal study; however, one double-blind, placebo-controlled study found no additive effects on CNS depression or safety related performance (Herberg 1993). Alternatively, a study of 10 subjects found that when alcohol and kava kava were combined, kava kava potentiated both the perceived and measured impairment compared to alcohol alone (Foo & Lemon 1997). Caution is advised when taking this combination together.

Barbiturates

Additive effects are theoretically possible. Use with caution and monitor drug dosage. However, interaction may be beneficial under professional supervision.

Benzodiazepines

Additive effects are theoretically possible. Use with caution and monitor drug dosage. However, interaction may be beneficial under professional supervision. The combination has been used successfully to ease symptoms of benzodiazepine withdrawal.

L-Dopa medication
Antagonistic effects are theoretically possible, thereby reducing the effectiveness of L-dopa. Avoid concurrent use unless under professional supervision until safety is confirmed.

Methadone and morphine
Additive effects with increased CNS depression are theoretically possible, so use with caution, although interactions may be beneficial under professional supervision.

Substrates for CYP2E1
Inhibition of CYP2E1 has been demonstrated in vivo — serum levels of CYP2E1 substrates may become elevated — use caution.

CONTRAINDICATIONS AND PRECAUTIONS
Endogenous depression — according to Commission E (Blumenthal et al 2000).

Although clinical studies indicate no adverse effects on vigilance, the herb's CNS effects may slow some individuals' reaction times, thereby affecting ability to drive a car or operate heavy machinery. Additionally, it should not be used by people with preexisting liver disease and long-term continuous use should be avoided unless under medical supervision. It should be used with caution in the elderly and in those with Parkinson's disease.

PREGNANCY USE
Safety is unknown.

PRACTICE POINTS/PATIENT COUNSELLING
- Kava kava is a scientifically proven treatment for the symptoms of anxiety and stress states. Its anxiety-reducing effects are similar to those of 15 mg oxazepam or 9 mg bromazepam; yet, physical tolerance and reduced vigilance have not been observed.
- It also reduces symptoms of anxiety related to menopause when used together with HRT, and reduces withdrawal symptoms associated with benzodiazepine discontinuation.
- It has anxiolytic, sedative, antispasmodic, analgesic and local anaesthetic activities.
- Although the herb is considered to have a low incidence of adverse effects, long-term use should be carefully supervised because of the possibility of developing adverse reactions.
- Rare hepatotoxic effects have been reported for methanolic and ethanolic extracts, whereas traditional aqueous extracts are considerably safer. The mechanism responsible remains elusive.

PATIENTS' FAQs
What will this herb do for me?
Kava kava is an effective herbal relaxant that reduces symptoms of anxiety and restlessness. It is also used to relieve anxiety in menopause, insomnia and symptoms of benzodiazepine withdrawal.

When will it start to work?
Anxiety-relieving effects are usually seen within the first few weeks of use.

Are there any safety issues?
Taking high doses long term has been associated with a number of side effects and should be avoided.

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Lavender

HISTORICAL NOTE Lavender, both the whole plant and its essential oils, have a long history of traditional use for a range of medical conditions. Lavender was used as an antiseptic in ancient Arabian, Greek and Roman medicines. Its generic name comes from the Latin *lavare*, to wash, and it was used as a bath additive as well as an antiseptic in the hospitals and sick rooms of ancient Persia, Greece and Rome (Blumenthal et al 2000) and as an antibacterial agent in World War I (Cavanagh & Wilkinson 2005). In the 17th century, Culpeper described lavender as having 'use for pains in the head following cold, cramps, convulsions, palsies and faintings' (Battaglia 1995). Lavender was also used traditionally to scent bed linen and to protect stored clothes from moths. This was such a well-accepted practice that the phrase 'laying up in lavender' was used metaphorically to mean 'putting away in storage' (Kirk-Smith 2003). Lavender is now widely used in perfumes, potpourri, toiletries and cosmetics, to flavour food as well as therapeutically. However, research produces a conflicting evidence base for lavender for a range of reasons, including the facts that the species of lavender is not always identified, that lavender is frequently adulterated, and that little attention has been paid to species other than *Lavandula angustifolia*, which is also known as true lavender. Lavender is commonly adulterated with related species that can vary in their chemical constituents. Spike lavender yields more oil, but is of lower quality than true lavender. Lavandin is a hybrid of spike lavender and true lavender.

COMMON NAME
Lavender

OTHER NAMES
Common lavender, English lavender, French lavender, garden lavender, Spanish lavender, spike lavender, true lavender

BOTANICAL NAME/FAMILY
Lavandula angustifolia (synonyms: *L. officinalis*, *L. vera*, *L. spica*); *L. dentata*; *L. latifolia*; *L. pubescens*; *L. stoechas*, *L multifida* (family Labiatae)

PLANT PARTS USED
Flower

CHEMICAL COMPONENTS
Lavender flowers contain between 1% and 3% essential oil. The oil is a complex mixture of many different compounds, the amounts of which can vary between species. The most abundant compounds include linalyl acetate (30–55%), linalool (20–35%), cineole, camphor, coumarins and tannins (5–10%) (Schulz et al 1998) together with 1,8-cineole, thymol and carvacrol (Aburjai et al 2005). Perillyl alcohol and D-limonene have been shown to exert anticancer effects (see clinical note). More recently, 39 constituents, accounting for 99% of total constituents, were extracted from *Lavandula multifida* (Rhaffari et al 2007). The main constituents were phenols such as thymol (32%), carvacrol

Clinical note — Perillyl alcohol and anticancer effects

Perillyl alcohol and D-limonene are monoterpenes found in lavender (also in cherries, mint and celery seeds) that have shown chemotherapeutic and chemoprotective effects in a wide variety of in vitro and animal models (Shi & Gould 2002) and are currently being examined in human clinical trials (Gould 1997, Kelloff et al 1999). Perillyl alcohol treatment has resulted in 70–99% inhibition of 'aberrant hyperproliferation', a late-occurring event preceding mammary tumorigenesis in vivo (Katdare et al 1997) and, together with limonene, perillyl alcohol has been shown to induce the complete regression of rat mammary carcinomas by what appears to be a cytostatic and differentiation process (Shi & Gould 1995). Perillyl alcohol has also been shown to inhibit human breast cancer cell growth in vitro and in vivo (Yuri et al 2004) and inhibit the expression and function of the androgen receptor in human prostate cancer cells (Chung et al 2006).

A variety of mechanisms has been proposed to explain these effects. The compounds may act via interfering with Ras signal transduction pathways that regulate malignant cell proliferation (Hohl 1996) and have been found to promote apoptosis in pancreatic adenocarcinoma cells (Stayrook et al 1997) and liver tumours in vivo (Mills et al 1995). Perillyl alcohol, together with D-limonene, has been found to preferentially inhibit HMG-CoA reductase in tumour cells (Elson et al 1999), as well as inhibit ubiquinone synthesis and block the conversion of lathosterol to cholesterol, which may add to its antitumour activity (Ren & Gould 1994). Limonene is oxidised by the CYP2C9 and CYP2C19 enzymes in human liver microsomes (Miyazawa et al 2002a) and there are reported sex-related differences in the oxidative metabolism of limonene by liver microsomes in rats (Miyazawa et al 2002b).

Although in vitro and animal studies have demonstrated the ability of perillyl alcohol to inhibit tumorigenesis in the mammary gland, liver and pancreas, the results are not yet conclusive and one animal study testing perillyl alcohol detected a weakly promoting effect early in nitrosamine-induced oesophageal tumorigenesis in rats (Liston et al 2003). In initial phase II clinical trials, perillyl alcohol administered orally, four times daily, at a dose of 1200 mg/m^2 had no clinical antitumour activity on advanced ovarian cancer (Bailey et al 2002) metastatic androgen-independent prostate cancer (Liu et al 2003) or metastatic colorectal cancer (Meadows et al 2002).

(27.77%) and *p*-cymene (15.72%), and *γ*-terpinene (9.54%). Phenols are not commonly found in lavender. These constituents give the oil significant antibacterial activity similar to ampicillin and tetracycline in a dose-dependent manner (Rhaffari et al 2007).

MAIN ACTIONS

The pharmacological actions of lavender and several of its constituents have been demonstrated. However, the true therapeutic benefit is controversial partly because many studies have methodological flaws and often combine lavender with massage and other therapies such as acupressure.

Sedative/anxiolytic

The sedative properties of the essential oil and its main constituents (linalool and linalyl acetate) were shown to have a dose-dependent effect in mice and to reverse caffeine-induced hyperactivity in mice (Buchbauer et al 1991, Lim et al 2005), as well as reduce stress, as indicated by modulation of adrenocorticotrophic hormone (ACTH), catecholamine and gonadotropin levels in experimental menopausal rats (Yamada et al 2005), and reduce cortisol responses in infant Japanese macaques (Kawakami et al 2002). Inhalation of lavender has also been shown to produce a dose-dependent anticonvulsant effect in both rats and mice (Yamada et al 1994).

In human trials, inhalation of lavender has been shown to induce relaxation and sedation (Schulz et al 1998) and to alter EEG responses (Diego et al 1998, Dimpfel et al 2004, Lee et al 1994, Sanders et al 2002, Yagyu 1994), as well as significantly decrease heart rate and increase high-frequency spectral components to produce calm and vigorous mood states in healthy volunteers (Kuroda et al 2005). Transdermal absorption of linalool without inhalation produced a decrease in systolic blood pressure and a smaller decrease of skin temperature with no effects on subjective evaluation of wellbeing in healthy human subjects (Heuberger et al 2004), and another study found that lavender scent was associated with lower fatigue following an anxiety-provoking task (Burnett et al 2004).

These positive studies are contrasted by studies with negative findings. Lavender aromatherapy did not significantly improve scores on the Hospital Anxiety and Depression Scale or the Somatic and Psychological Health Report (SPHERE) in a RCT of 313 patients undergoing radiotherapy (Graham et al 2003) and a study of 169 subjects, including both depressed and non-depressed subjects, showed that lavender increased fatigue, tension, confusion and total mood disturbance, and decreased vigour (Goel & Grasso 2004).

Antimicrobial

Various in vitro data suggest that lavender oil has antibacterial activity (Dadalioglu & Evrendilek 2004, Larrondo et al 1995), including against methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococcus (VRE) (Nelson 1997), antifungal activity (Inouye et al 2001), including against *Aspergillus nidulans* and *Trichophyton megatrophytes* (Daferera et al 2000) and mitocidal activity (Perrucci et al 1996, Refaat et al 2002), with

both lavender and linalool having fungistatic and fungicidal activities against *Candida albicans* strains at high concentrations and inhibiting germ tube formation and hyphal elongation at low concentrations, suggesting that it may be useful for reducing fungal progression and the spread of infection in host tissues (D'Auria et al 2005). Lavender has been shown to be active alone and to work synergistically with tea tree oil against the fungi responsible for tinea and onychomycosis (Cassella et al 2002). However, effective vapour concentrations have not yet been established for aromatherapy use.

The fungistatic properties of linalool have led to the suggestion that it could be used to complement environmental measures in preventing fungal contamination in storage areas of libraries (Rakotonirainy & Lavedrine 2005).

Carminative

Linalool, one of lavender's major components, demonstrated spasmolytic activity when tested on an in vitro preparation of guinea-pig ileum smooth muscle (Lis-Balchin & Hart 1999).

Antineoplastic effects

In vitro and animal studies suggest that perillyl alcohol and D-limonene (see Clinical note) may have useful chemotherapeutic and chemoprotective effects in a range of cancers, including cancers of the colon, liver, lung, breast, pancreas and prostate, as well as in melanoma (Micromedex 2003). These results have not yet been confirmed in human studies.

OTHER ACTIONS

When applied topically, lavender oil has rubefacient properties (Fisher & Painter 1996) and is thought to have analgesic, antihistaminic and anti-inflammatory activities. A small study comparing the effects of a bath containing lavender oil, synthetic lavender oil and distilled water in reducing perineal discomfort after childbirth found lower mean discomfort scores in the lavender group; however, the differences between groups were not significant (Cornwell & Dale 1995).

Traditionally, lavender oil is considered to have a balancing effect on the CNS, acting as an aromatic stimulant or calming agent.

Extracts of *L. multifida* have been found to have topical anti-inflammatory activity in mice, with some extracted compounds having activity comparable to that of indomethacin (Sosa et al 2005). At high concentrations (0.1%), lavender oil has also been found to suppress TNF-alpha-induced neutrophil adherence (Abe et al 2003). Lavender has also demonstrated powerful antioxidant activity (Gulcin et al 2004), as well as antimutagenic activity (Evandri et al 2005) and antiplatelet and antithrombotic properties demonstrated both in vitro and in vivo (Ballabeni et al 2004).

CLINICAL USE

Although few scientific or clinical studies have been conducted with lavender oil, much of the evidence supporting its use is based on the known pharmacological actions of the constituents and a long history of traditional use.

Anxiety, insomnia and mood enhancement

A number of controlled trials and observational studies suggest that inhalation of ambient lavender oil has a relaxing effect and is able to reduce anxiety and improve mood, concentration and sleep.

In a study of 31 healthy volunteers, intermittent exposure to ambient lavender oil over a 30-minute period was found to increase the percentage of deep or slow-wave sleep in men and women with corresponding reports of higher vigour the morning after lavender exposure (Goel et al 2005). That study also reported gender-specific effects with increased stage 2 (light) sleep, as well as decreased rapid-eye movement sleep and decreased amount of time needed to reach wakefulness after first falling asleep in women, and opposite effects in men. In a 4-week randomised, double-blind pilot study, lavender tincture (1:5 in 50% alcohol) 60 drops/day was not as effective as imipramine for treating depression; however, a combination of lavender tincture and imipramine was found to be more effective than imipramine alone with better and earlier improvement (Akhondzadeh et al 2003). In another randomised, placebo-controlled pilot study, using a crossover design, lavender aromatherapy produced a non-significant improvement in insomnia compared with exposure to almond oil (Lewith et al 2005). A case study of four geriatric patients with impaired sleep also found that lavender aromatherapy increased sleep time and was comparable in effectiveness to hypnotics or tranquillisers (Hardy et al 1995). A double-blind study of 140 patients found that an essential oil spray or gargle containing lavender with 14 other essential oils significantly reduced snoring as reported by bed partners (Prichard 2004).

In hospitalised patients, aromatherapy with lavender oil was found to significantly reduce anxiety in a study of 14 female haemodialysis patients (Itai et al 2000). Another controlled trial of 200 subjects found that lavender aromatherapy reduced anxiety and improved mood in patients waiting for dental treatment (Lehrner et al 2005).

A number of studies have examined the use of lavender aromatherapy and massage with lavender oil (see below) for reducing agitation in dementia patients; however, these studies are generally small and results have been mixed. A placebo-controlled study found that lavender aromatherapy effectively reduced agitated behaviour in 15 patients with severe dementia (Holmes et al 2002), but it had no effect on reducing agitation in another controlled trial of seven severely demented patients (Snow et al 2004), nor was there effect on reducing resistive behaviour in 13 people with dementia in a residential aged care facility (Gray & Clair 2002).

In a RCT involving 80 non-depressed women, adding lavender oil to a bath was found to enhance the general mood-enhancing effects of daily bathing and produce a reduction in pessimism (Morris 2002). It has been suggested that the relaxing effects may be useful in the treatment of chronic

pain (Buckle 1999), and this is supported by a study reporting that while lavender did not elicit a direct analgesic effect, it did alter affective appraisal of the pain experience with retrospective impression of pain intensity and pain unpleasantness from experimentally induced heat, pressure and ischaemic pain being reduced after treatment with lavender aromatherapy (Gedney & Glover 2004).

When used in combination with massage

Overall, the evidence supporting the use of lavender oil in massage is encouraging; however, most studies are relatively small and there are mixed reports of its efficacy.

A controlled trial of 122 patients found that massage with lavender oil improved mood and perceived levels of anxiety in 122 intensive care patients (Dunn et al 1995). In a RCT, eight sessions of acupressure using lavender essential oil over 3 weeks was found to be effective in relieving pain, neck stiffness and stress in 32 adults with subacute non-specific neck pain (Yip & Tse 2006). In another controlled trial, a 2-week lavender aromatherapy hand massage program produced significant improvements in emotion and aggressive behaviour in elderly people with Alzheimer's type dementia (Lee 2005). Alternatively, one RCT involving 42 subjects found that the addition of lavender essential oil did not appear to increase the beneficial effects of massage for patients with advanced cancer (Soden et al 2004).

Use in animals

Lavender aromatherapy has also been found to produce increased resting and reduced movement and vocalisation in dogs housed in a rescue shelter (Graham et al 2005). Daily essential oil baths using *L. angustifolia* for 14 days led to lower stress and trait anxiety in both the experimental and the control groups but a larger effect occurred in the lavender group ($n = 37$) (Morris 2008).

Lavender aromatherapy reduced serum cortisol (a marker of stress hormones) and improved coronary flow velocity reserve (CFVR) in healthy men suggesting that lavender aromatherapy has relaxation effects and may have beneficial acute effects on coronary circulation (Shiina et al 2008). CFVR was measured with non-invasive transthoracic Doppler echocardiography (TTDE). CFVR was assessed at baseline and immediately after lavender aromatherapy (four drops of essential oil diluted with 20 mL of hot water and inhaled for 30 minutes). Simultaneously, serum cortisol was measured.

Another study of healthy young women found that lavender aromatic treatment induced not only relaxation but also increased arousal level in these subjects as measured by continuous electrocardiographic (ECG) monitoring before and after (10, 20, 30 minutes) the lavender fragrance stimuli (Duan et al 2007). Increases in the parasympathetic tone were observed after the lavender fragrance stimulus seen as increases in the heart function component and decreases in the low frequency (LF)/high frequency (HF). Additional measurement with positron emission tomography demonstrated the regional metabolic activation in the orbitofrontal, posterior cingulate gyrus, brainstem, thalamus and cerebellum, as well as the reductions in the pre/post-central gyrus and frontal eye field.

Commission E supports the use of oral lavender in mood disturbances such as restlessness and insomnia (Blumenthal et al 2000).

Dementia care

Managing difficult behaviours in aged care facilities is very challenging. A number of researchers have shown reductions in agitated behaviour using lavender in massage, baths, vaporisers and on bedclothes (Bowles et al 2005, Holmes et al 2002, Lin et al 2007, Smallwood et al 2001). These studies generally show positive effects; however, they are difficult to interpret because of the individual nature of behaviour and odour effects on individuals as well as the methodological differences among the studies.

Most recently, a crossover randomised trial of 70 Chinese older adults with dementia demonstrated that lavender inhalation for 3 weeks significantly decreased agitated behaviours (Lin et al 2007). As this patient population is particularly vulnerable to side effects of psychotropic medications, aromatherapy using lavender may offer an attractive alternative option.

Improved concentration

In a RCT, exposure to lavender aromatherapy during breaks resulted in significantly higher concentration levels during the afternoon period when concentration was found to be lowest in a control group (Sakamoto et al 2005). Lavender oil aromatherapy has also been found to reduce mental stress and increase arousal rate (Motomura et al 2001), to elicit a subjective sense of 'happiness' (Vernet-Maury et al 1999) and to produce increased relaxation, less depressed mood and faster and more accurate mathematical computations (Field et al 2005). In a RCT, lavender aromatherapy tended to enhance calculating speed and calculating accuracy in female but not male subjects (Liu et al 2004), but results from another study suggest that lavender reduced working memory and impaired reaction times for both memory and attention-based tasks compared with controls (Moss et al 2003).

A controlled study of dementia patients found that a blend of lavender, sweet marjoram, patchouli and vetiver essential oils in a cream massaged 5 times/day for 4 weeks onto the bodies and limbs of 56 aged care facility residents with moderate-to-severe dementia produced a small but significant improvement in mini mental state examination associated with increased mental alertness and awareness and resistance to nursing care procedures compared with massage with cream alone (Bowles et al 2002).

Dyspepsia and bloating

Although there have been no clinical trials to investigate its use, lavender is commonly recommended for gastrointestinal disorders as a carminative and antiflatulent to soothe indigestion, colic, dyspepsia

and bloating (Blumenthal et al 2000). Based on the antispasmodic actions of a key constituent, linalool, lavender may be useful in these conditions. No controlled clinical studies could be located to determine its effectiveness for these indications.

Alopecia

A RCT of scalp massage using thyme, rosemary, lavender and cedarwood essential oils in 86 patients with alopecia areata found a significant improvement in hair growth after 7 months (Hay et al 1998). Although the efficacy of lavender as a standalone treatment was not clarified with this trial, it is known that the herb has some antibacterial and antifungal activity that may play a role. In a single case study, topical application of lavender, together with other essential oils, was reported to assist in treating scalp eczema (De Valois 2004).

Perineal discomfort following childbirth

A RCT in 635 women following childbirth found that using lavender oil in bath water was safe and pleasant to use and that there was a tendency towards lower discomfort scores between the third and fifth day (Dale & Cornwell 1994). In that study, six drops of pure lavender oil was added to the bath.

Dysmenorrhoea

Aromatherapy applied topically in the form of an abdominal massage using two drops of lavender (*Lavandula officinalis*), one drop of clary sage (*Salvia sclarea*), and one drop of rose (*Rosa centifolia*) in 5 cc of almond oil significantly decreased the severity of menstrual cramps, according to a randomised, placebo-controlled study (Han et al 2006). The study involved 67 female college students who rated their menstrual cramps to be greater than 6 on a 10-point visual analogue scale, who had no systemic or reproductive diseases, and who did not use contraceptive drugs.

Insect bites

In vitro and animal studies suggest that lavender oil inhibits immediate-type allergic reactions by inhibition of mast cell degranulation (Kim & Cho 1999).

OTHER USES

Lavender has a long history of use as a sedative, an antidepressant, an antimicrobial agent, a carminative (smooth muscle relaxant), a topical analgesic agent for burns and insect bites (Cavanagh & Wilkinson 2002) and an insect repellent. Lavender has also been used to treat migraines and neuralgia, as an astringent to treat minor cuts and bruises, and is used externally for strained muscles, as well as acne, eczema and varicose ulcers (Fisher & Painter 1996). It is also used in a gargle for loss of voice.

A recent study in Hong Kong using eight sessions of acupoint stimulation followed by acupressure with lavender oil over 3 weeks compared with a placebo demonstrated effective short-term relief of neck pain (Yip & Tse 2005). Pain, stress, neck stiffness, tension and mobility all improved.

In Australia, lavender essential oil is the most popular aromatherapy oil, out-selling the second most popular (orange) oil by more than seven times (F Kheery (In Essence) pers. commun. 2002). It is often combined with bergamot and cedarwood oils for relieving anxiety and stress and combined with marjoram to induce sleep. There is a lack of definitive evidence for the effects of lavender on sleep. However, small comparative studies using lavender oil and placebo and case studies suggest a trend towards improved sleep quality and duration (Diego et al 1998, Hardy et al 1995).

Lavender oil has also been studied for veterinary applications. The ambient odour of lavender reduced travel-induced excitement in dogs, according to a study involving 32 dogs with a history of travel-induced excitement in owners' cars (Wells 2006). Dogs exposed to lavender spent significantly more time resting and sitting and less time moving and vocalising during the experimental condition.

DOSAGE RANGE

Probably no other herb is available in as many forms as lavender.

- Infusion (tea): 1.5 g dried flowers in 150 mL water, which is 1–2 teaspoons lavender flowers or leaves in one cup of boiling water steeped for 5–10 minutes and strained before drinking.
- Internal: 1–4 drops (20–80 mg) on a sugar cube.
- Liquid extract (1:2): 2–4.5 mL/day.
- External use: mix 20 drops of oil with 20 mL of carrier oil such as almond oil. May be applied undiluted to insect bites or stings.
- As a bath additive: 20–100 g lavender flowers are commonly steeped in 2 L boiling water, strained, and then added to the bathwater.
- Aromatherapy: use 2–4 drops of lavender oil in a suitable oil diffuser or on a pillow case to assist sleep.

Lavender oil is quickly absorbed by the skin and constituents linalool and linalyl acetate have been detected in the blood 5 minutes after administration. Blood levels peak after 19 minutes and are negligible by 90 minutes.

TOXICITY

McGuffin (1997) lists lavender as a Class I herb, a classification which represents herbs that can be 'safely consumed when used appropriately'. The acute oral toxicity dose (LD_{50}) in rats for lavender and linalool are 5 g/kg and 2.8 g/kg, respectively and the acute dermal toxicity in rabbits is 5 g/kg and 5.6 g/kg, respectively (Kiefer 2007). These doses would translate to approximately 350 g lavender oil or 1.5 cups.

Although there are no specific reports of toxicity, it is suggested that no more than two drops be taken internally. There is a potential for irritant or allergenic skin reactions with the topical use of lavender oil, as it has been found to be cytotoxic to human skin cells in vitro (endothelial cells and fibroblasts) at a concentration of 0.25% v/v, possibly due to membrane damage. The activity

of linalool was found to reflect the cytotoxicity of the whole oil, whereas the cytotoxicity of linalyl acetate was found to be higher than that of the oil, suggesting suppression of its activity by an unknown factor in the oil (Prashar et al 2004). Three case reports have been published of gynaecomastia developing in boys aged four, seven and ten following regular topical use of lavender-containing products (soap, shampoo and lotions) (Henley et al 2007). Henley et al postulated that lavender has oestrogenic and antiandrogenic effects on several different cell lines. The implications for clinical practice and aromatherapy are unknown.

Skin sensitivity to lavender might develop with increased exposure and prolonged use (Sugiura et al 2000).

SIGNIFICANT INTERACTIONS

Controlled studies are not available; therefore, interactions are based on evidence of activity and are largely theoretical and speculative.

Pharmaceutical sedatives

Theoretically, lavender can potentiate the effects of sedatives, so observe patients taking this combination closely — beneficial interaction possible under professional supervision.

Antidepressants

Lavender tincture may have additive effects when used with these medicines — beneficial interaction possible.

PREGNANCY USE

No restrictions known for external use.

Safety of internal use has not been scientifically established.

PRACTICE POINTS/PATIENT COUNSELLING

- The active part of lavender is the volatile oil, which has relaxing, sedative, antispasmodic and antiseptic activity.
- Lavender can be taken as a tincture or tea, or the oil can be applied topically, used in baths or inhaled from a diffuser.
- It is advised that topical preparations be tested on a small area of skin before widespread application.
- Lavender has traditionally been used for sleep disorders, anxiety and nervous stomach, as well as to treat minor cuts, burns, bruises and insect bites and is commonly found in cosmetics and toiletries.
- Lavender contains substances that are currently being studied for cancer prevention.
  - Ambient lavender induces a relaxation response in healthy people, the elderly with dementia and agitation and also dogs with travel-induced excitement.
  - Abdominal massage with lavender oil (in combination with several others) has been shown to reduce menstrual cramps to a better degree than a non-aromatherapy oil.

PATIENTS' FAQs

What will this herb do for me?

Lavender oil is used to assist in relaxation, digestive problems and as first aid for minor skin conditions. Ambient lavender induces a relaxation response in healthy people and the elderly with dementia and agitation and also calms dogs during travel. Used as part of an aromatherapy massage, it also has antispasmodic activity.

When will it start to work?

As a relaxant, effects may be felt on the first day of use, but this will depend on the dose and form used.

Are there any safety issues?

Although lavender has not been scientifically studied as extensively as some other herbal medicines, historical use suggests that it is generally safe.

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Lemon balm

HISTORICAL NOTE Lemon balm was used in ancient Greece and Rome as a topical treatment for wounds. In the Middle Ages it was used internally as a sedative and by the 17th century, English herbalist Culpeper claimed it could improve mood and stimulate clear thinking. Nowadays, it is still used to induce a sense of calm and help with anxiety, but is also added to cosmetics, insect repellants, furniture polish and food.

COMMON NAME
Lemon balm

OTHER NAMES
Balm mint, bee balm, blue balm, common balm, cure-all, dropsy plant, garden balm, sweet balm

BOTANICAL NAME/FAMILY
Melissa officinalis (family Lamiaceae)

PLANT PART USED
Aerial parts

CHEMICAL COMPONENTS
Flavonoids, phenolic acids, tannins, triterpenes, essential oil and sesquiterpenes. Of note, the herb contains citronellal, caffeic acid, eugenol, rosmarinic acid and choline (Wake et al 2000). Growing and harvesting methods have a major influence on

the amount of volatile oil present in the leaves. It has been found that the oil content in the herb is highest in the top third and lowest in the bottom two-thirds (Mrlianova et al 2002).

MAIN ACTIONS

Anxiolytic and sedative

Over the years, a number of studies involving rodents have suggested specific anxiolytic or sedative effects (Kennedy et al 2002, Soulimani et al 1991, Abuhamdah et al 2008). A number of possible active components of the dried leaf and essential oil of the herb may be responsible for these effects, such as eugenol and citronellol, which bind to GABA-A receptors and increase the affinity of GABA to receptors (Aoshima & Hamamoto 1999). Rosmarinic acid has also been shown to possess anti-anxiety properties in vivo (Pereira et al 2005)

Antiviral

A lemon balm extract was found to have significant virucidal effects against HSV-1 within 3 and 6 hours of treatment in vitro and in animal tests (Dimitrova et al 1993). The volatile oils from *M. officinalis* have also been shown to inhibit the replication of HSV-2 in vitro (Allahverdiyer et al 2004).

Two more recent studies have demonstrated the antiviral effects of lemon balm against HSV in plaque reduction assays. One study used an essential oil preparation, whilst the other used an aqueous extract (Schnitzler et al 2008, Nolkemper et al 2006). Both studies demonstrated > 90% inhibition of plaque formation for HSV-1 and HSV-2, and in one study an acyclovir-resistant strain of HSV-1 was reduced by 85% (Nolkemper et al 2006). Both studies also found that lemon balm affected HSV before adsorption, but had no effect on viral replication.

Lemon balm has demonstrated a virucidal effect against HIV-1 in T-cell lines and macrophages in vitro (Geuenich et al 2008). Inhibitory activity against HIV-1 reverse transcriptase has also been shown (Yamasaki et al 1998).

Antibacterial and antifungal

One in vitro study found that lemon balm extract exhibited activity against bacteria, filamentous fungi and yeasts (Larrondo et al 1995). It is likely that the constituent eugenol is chiefly responsible, as it has well established antibacterial activity against such organisms as *Escherichia coli* and *Staphylococcus aureus* (Walsh et al 2003).

Cholinergic

Lemon balm exhibits CNS acetylcholine receptor activity, with both nicotinic and muscarinic binding properties (Wake et al 2000). In vitro data has demonstrated that lemon balm is a weak inhibitor of acetylcholinesterase and has a moderate affinity to the GABA-A benzodiazepine receptor site (Salah & Jager 2005). This indicates that lemon balm may have a role to play in the treatment of Alzheimer's disease and epilepsy. However, a 2003 randomised, double-blind, placebo-controlled, crossover trial demonstrated that lemon balm did not inhibit cholinesterase. The trial demonstrated improved cognitive function and mood and concluded that for these reasons it was a valuable adjunct to Alzheimer's therapy (Kennedy et al 2003).

> ***Clinical note***
> Long before the current biologically based theory of cholinergic abnormalities in Alzheimer's dementia emerged, Western European medicine systems have traditionally used several herbs that are now known to exert cholinergic activity (such as sage and lemon balm) for their dementia-treating properties.

Anti-inflammatory, analgesic and antispasmodic

The plant extract exerts analgesic activity at high doses in vivo (Soulimani et al 1991). Two constituents in lemon balm have documented anti-inflammatory activity, achieved through different mechanisms of action. Rosmarinic acid, a naturally occurring constituent found in *M. officinalis*, inhibits several complement-dependent inflammatory processes (Englberger et al 1988, Peake et al 1991). Eugenol, another important component, inhibits COX-1 and -2 activities in vitro (Huss et al 2002, Kelm et al 2000).

Both the whole volatile oil and its main component citral have demonstrated antispasmodic ability on isolated rat ileum (Sadraei et al 2003). Similarly, both the aqueous extract and rosmarinic acid component demonstrated vasorelaxant properties on isolated rat aorta (Ersoy et al 2008). An in vivo study has shown both an extract of lemon balm and the herbal formulation ColiMil® (chamomile, fennel and lemon balm) may delay gastric emptying (Capasso et al 2007). The group treated with lemon balm exhibited 36% inhibition, chamomile 28% and fennel 9% as compared to 45% for the ColiMil® group, suggesting a synergistic action.

Antioxidant

Lemon balm has shown antioxidant activity in several studies (Apak et al 2006, Canadanovic-Brunet et al 2008, Ferreira et al 2006, Hohmann et al 1999, Lopez et al 2007). According to a 2003 study, concentrations of antioxidants within lemon balm are >75 mmol/100 g (Dragland et al 2003).

Cardiovascular effects

Aqueous extracts of lemon balm have been shown to slow cardiac rate but not alter the force of contraction in isolated rat hearts (Gazola et al 2004). An extract of lemon balm reduced blood cholesterol and lipid levels in rats fed a high fat and alcohol diet (Bolkent et al 2005). Interestingly, the extract also increased glutathione levels and reduced lipid peroxidation in the liver, demonstrating a hepatoprotective effect.

OTHER ACTIONS

Lemon balm inhibits the binding of TSH to thyroid plasma membranes in vitro and the extrathyroidal enzymic T4-5'-deiodination to T3 (Auf'mkolk

et al 1984a). Antitumour activity has also been demonstrated (Chlabicz & Galasinski 1986, Dudai et al 2005, Galasinski 1996, Galasinski et al 1996).

CLINICAL USE

In clinical practice, lemon balm is often prescribed in combination with other herbal medicines. As a reflection of this, many clinical studies have investigated the effects of lemon balm as an ingredient of a herbal combination, making it difficult to determine the efficacy of this herb individually.

Anxiety

In 2005 a small double-blind, placebo-controlled, randomised, crossover trial involving 18 healthy volunteers investigated the effects of a whole extract of lemon balm in two different doses (300 and 600 mg) and found a significant reduction in stress in the volunteers taking the larger dose (Kennedy et al 2004).

The essential oil of lemon balm has also been investigated under double-blind placebo-controlled conditions and found to be a safe and effective treatment for clinically significant agitation in people with severe dementia (Ballard et al 2002). The trial, which involved 71 subjects, found that after 1 month's treatment, patients were less agitated, less socially withdrawn and spent more time in constructive activities than those in the placebo group.

Commission E approves the use of lemon balm in the treatment of anxiety and restlessness (Blumenthal et al 2000).

In combination

A combination of lemon balm and valerian (*Valeriana officinalis*) was examined for acute effects on anxiety in a double-blind, placebo-controlled, randomised, crossover experiment of 24 individuals (Kennedy et al 2006). Three separate concentrations of the standardised product (600 mg, 1200 mg, 1800 mg) were given on separate days after a 7-day wash-out period. Any changes to mood and anxiety were assessed pre-dose and at 1, 3 and 6 hour intervals. Interestingly, the lower dose (600 mg) was shown to decrease anxiety levels whereas the highest dose (1800 mg) increased anxiety. The exact effect of lemon balm in this preparation is hard to determine.

Cognitive function

Lemon balm has been used for centuries to improve cognitive function and encouraging results from a 2002 clinical study confirm that it can influence memory.

The randomised, double-blind crossover study involving 20 healthy young volunteers found that single doses of lemon balm were able to modulate both mood and cognitive performance in a dose- and time-dependent manner (Kennedy et al 2002). In this study, treatment with the lowest dose (300 mg) increased self-rated 'calmness' within 1 hour whereas the 600 mg and 900 mg doses produced significant effects on memory task performance, observable at both 2.5 hours and 4 hours after administration. The highest tested dose (900 mg) was found to significantly reduce alertness within 1 hour, suggesting a dose–response effect.

Alzheimer's disease

A randomised, double-blind, placebo-controlled trial demonstrated the efficacy and safety of *M. officinalis* in 42 patients aged 65–80 with mild to moderate Alzheimer's disease who were given 60 drops/day for 4 months (Akhondzadeh et al 2003). Outcome measures included significantly better cognition and reduced agitation.

Insomnia

In clinical practice, lemon balm is often prescribed in combination with other herbs such as valerian in the treatment of insomnia. As a reflection of this, a randomised, double-blind multicentre study investigated the effects of a commercial valerian and lemon balm herbal combination (Songha Night) in 98 healthy subjects (Cerny & Schmid 1999). Treatment was administered over a 30-day period and consisted of 3 tablets taken half an hour before bedtime, providing a total dose of 1–6 g valerian and 1–2 g lemon balm. Herbal treatment was found to significantly improve sleep quality and was well tolerated.

Another randomised, double-blind crossover study found that the same combination of valerian and lemon balm taken over 9 nights was as effective as triazolam in the treatment of insomnia (Dressing et al 1992). The dose used was equivalent to 1.4 g dried valerian and 0.9 g dried lemon balm.

As with all herbal combination studies, it is difficult to determine the contribution each individual herb made to the end result. As such, these studies are encouraging but the role of lemon balm as a stand-alone treatment for insomnia remains unclear.

Commission E approves the use of lemon balm in the treatment of insomnia (Blumenthal et al 2000).

Gastrointestinal conditions associated with spasm and nervousness

To date, only studies using lemon balm in combination with other herbs are available.

A pilot study investigated the effects of Carmint, containing lemon balm, spearmint and coriander, in 32 patients with irritable bowel syndrome (Vejdani et al 2006). Patients were randomly assigned Carmint or placebo, plus Loperamide or psyllium (based on their IBS subtype) for 8 weeks. The severity and frequency of abdominal pain and bloating were significantly lower in the Carmint group as compared to placebo at the end of the 8 weeks. A larger follow-up trial is needed to confirm these results.

A 15-day open study involving 24 subjects with chronic non-specific colitis investigated whether a combination of lemon balm, St John's wort, dandelion, marigold and fennel could provide symptom relief (Chakurski et al 1981). Excellent results were obtained by the end of the study, with

herbal treatment resulting in the disappearance of spontaneous and palpable pains along the large intestine in 95.83% of patients. A double-blind study using a herbal tea prepared from chamomile, lemon balm, vervain, licorice and fennel in infantile colic has also been conducted. A dose of 150 mL offered up to three times daily was found to eliminate symptoms of colic in 57% of infants, whereas placebo was helpful in only 26% after 7 days' treatment (Weizman et al 1993).

A randomised, double-blind, placebo-controlled trial was conducted to examine the effectiveness of ColiMil (lemon balm, chamomile and fennel) in 93 breast fed infants with colic (Savino et al 2005). The infants were randomised into two groups to receive either ColiMil or placebo both twice a day at 5pm and 8pm before feeding (2 mL/kg/day) for 7 days. A reduction in crying time was observed in 85.4% subjects in the active treatment group as compared to 48.9% for placebo ($P < 0.005$). This is a significant result, especially considering the treatment period was only seven days. No side effects were reported. Commission E supports the use of lemon balm for functional gastrointestinal conditions (Blumenthal et al 2000).

Herpes simplex type I — external use

The topical use of lemon balm preparations for HSV infection is very popular in Europe. Results from a randomised double-blind study in 66 subjects with a history of recurrent herpes labialis (> 3 episodes/year) found that standardised lemon balm ointment (700 mg crude herb per gram) applied four times daily for 5 days significantly shortened healing time, prevented infection spread and produced rapid symptom relief (Koytchev et al 1999). Decreased symptoms and increased rate of healing were also observed in another double-blind study of lemon balm cream in 116 subjects (Woelbling & Leonhardt 1994).

OTHER USES

Animal studies have identified dose-dependent anti-ulcerogenic activity for lemon balm extract, which has been histologically confirmed. This activity is associated with a reduced acid output and an increased mucin secretion, an increase in PGE_2 release and a decrease in leukotrienes (Khayyal et al 2001).

DOSAGE RANGE

- Fresh herb: 1.5–4.5 g two–three times daily.
- Infusion: 1.5–4.5 g in 150 mL water.
- Fluid extract (1:1) (g/mL): 6–12 mL/day.
- Ointment: 700 mg/g ointment applied four times daily for herpes simplex infection.

TOXICITY

Not known.

ADVERSE REACTIONS

Lemon balm is well tolerated according to one double-blind, randomised crossover study (Kennedy et al 2002).

SIGNIFICANT INTERACTIONS

Controlled clinical studies are not available, so interactions are speculative and based on evidence of activity.

Barbiturates

Increased sedative effects: one animal study (Soulimani et al 1991) found that concomitant administration of lemon balm extract with pentobarbital produced an increased sedative effect — observe patients taking this combination.

Cholinergic drugs

Additive effects are theoretically possible and may be beneficial — observe patients taking this combination.

CONTRAINDICATIONS AND PRECAUTIONS

Hypothyroidism — one in vitro study found that an extract of *M. officinalis* inhibited both the extrathyroidal enzymic T4-5'-deiodination to T3 and the T4-5'-deiodination (Auf'mkolk et al 1984b). Whether this has any clinical significance has yet to be determined.

PREGNANCY USE

Safety has not been scientifically established and is unknown.

PATIENTS' FAQs

What will this herb do for me?

Lemon balm has several different actions and is used for a number of different conditions. Taking the herb internally may help reduce anxiety and improve mood and mental concentration. When taken together with valerian, it can relieve insomnia. It may also relieve stomach spasms associated with nervousness, or in chronic, non-specific colitis when taken as part of a specific herbal combination. Melissa cream applied four times daily to herpes simplex infections can reduce symptoms, accelerate healing and reduce the chance of the infection spreading.

PRACTICE POINTS/PATIENT COUNSELLING

- Lemon balm has been used traditionally to treat insomnia, irritability, restlessness, anxiety and dementia. It is also used to relieve gastrointestinal symptoms associated with spasms and nervousness.
- Used topically as a cold sore treatment, it significantly reduces symptoms, shortens the healing period and prevents infection spread. It may be suitable both as an active treatment and as a preventative agent in cases of chronic recurrent herpes simplex infections.
- Lemon balm may have some anti-inflammatory and antispasmodic activity.
- The essential oil is used in aromatherapy to relieve anxiety and promote calm and a sense of wellbeing, which has been confirmed in one clinical study.
- One clinical study has found that it can modulate both mood and cognitive performance in a dose- and time-dependent manner.

When will it start to work?

Approximately one month's treatment with the essential oil is required for calming effects on agitation in dementia to be seen. Taken internally with valerian, effects on sleep may be seen after 9 days' use. Improved memory occurred within 2.5 hours according to one study; however, it is not known if and when effects are seen in dementia. Melissa cream has been shown to significantly reduce symptoms of herpes simplex within 2 days, when applied four times daily.

Are there any safety issues?

One study using lemon balm in tablet form found that it was well tolerated. Drug interactions are theoretically possible and this herb should be used cautiously in people with hypothyroidism.

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Licorice

HISTORICAL NOTE Licorice root has been used in Europe since prehistoric times, and its medicinal use is well documented (Fiore et al 2005). References to licorice date back to approximately 2500 BC on Assyrian clay tablets and Egyptian papyri. It has been used as both a food and a medicine since ancient times. The genus name, meaning 'sweet root', is attributed to the first century Greek physician Dioscorides. The herb is also popular in traditional Chinese and Ayurvedic medicines (Blumenthal et al 2000).

OTHER NAMES

Liquorice, licorice root, Chinese licorice, sweet root, gan cao, kanzo, kanzoh, radix glycyrrhizae, yashimadhu, yasti-madhu, alcacuz.

BOTANICAL NAME/FAMILY

Glycyrrhiza glabra L. (family Leguminosae)

There are around 30 species of *Glycyrrhiza* spp. so *G. glabra* should be differentiated from other medicinally used herbs such as: *G. uralensis* (synonyms: Chinese licorice, gan cao, licorice root, sweet root), *G. inflata* (synonyms: gan cao, zhigancao), *G. pallidiflora*, *G. glandulifera*, *G. pallida*, *G. typica* and *G. violacea*, although some studies do not always clearly state which form is used. In addition, there are three varieties of *G. glabra*: var. *violacea* (Persia, Turkey), var. *gladulifera* (Russia) and var. *typical* (Spain, Italy) (Asl & Hosseinzadeh 2008).

PLANT PARTS USED

Root and stolon

CHEMICAL COMPONENTS

Licorice contains several triterpenoid saponins (4–20%), the most studied of which is glycyrrhizin (GL, also known as glycyrrhizic acid or glycyrrhizinic acid), which is a mixture of potassium and calcium salts of glycyrrhetinic acid (GA). Other triterpenes include: liquiritic acid, glycyrretol, glabrolide and isoglabrolide (Asl & Hosseinzadeh 2008).

Other important constituents include: flavonoids (isoflavonoids, liquiritin, isoliquiritin, liquiritigenin, formononetin, glabridin, rhamnoliquiritin, neoliquiritin and the chalcones [isoliquiritigenin, licochalcone A and B]); sterols (beta-sitosterol, dihydrostigmasterol); polysaccharides (arabinogalactans); coumarins (liqcoumarin, glabrocoumarone A and B, herniarin, umbelliferone, glycerin, glycocoumarin, licofuranocoumarin, licopyranocoumarin and glabrocoumarin); phenols, fatty acids, glabrol; amines; glucose, sucrose; resin; and volatile oil. 5,8-Dihydroxy-flavone-7-*O*-beta-D-glucuronide, glychionide A, 5-hydroxy-8-methoxyl-flavone-7-*O*-beta-D-glucuronide, glychionide B, hispaglabridin A, hispaglabridin B, 4′-*O*-methylglabridin and 3′-hydroxy-4′-*O*-methylglabridin, glabroisoflavanone A and B and glabroisoflavanone B have also been isolated (Asl & Hosseinzadeh 2008, Blumenthal et al 2000).

Glycyrrhiza glabra should be differentiated from other species such as *G. inflata* and *G. uralensis*. While the constituent properties of *G. glabra* resemble that of *G. inflata*, they are not similar to *G. uralensis*. Furthermore, there are species-specific typical constituents including glabridin (*G. glabra*), licochalcone A (*G. inflata*) and glycycoumarin (*G. uralensis*) that may influence the pharmacological effects (Kondo et al 2007). Additionally, among different samples of *G. glabra* there may be significant differences in the content of active constituents and biological activity (Statti et al 2004). The lack of

Clinical note — GL, GA and side effects

GL is mainly absorbed after presystemic hydrolysis to GA (18-beta-glycyrrhetinic acid (glycyrrhetic acid; the aglycone of GL)). On excretion via the bile it may be reconjugated to GA by commensal bowel flora and then reabsorbed (Gunnarsdottir & Johannesson 1997, Hattori et al 1983, Ploeger et al 2001). GL and GA are associated with the side effects encountered with high-dose or long-term licorice use, such as elevated blood pressure and fluid retention. In people with prolonged gastrointestinal transit time, GA can accumulate after repeated intake. As GA is 200- to 1000-fold more powerful in inhibiting 11-beta-hydroxysteroid dehydrogenase (11HSD) than GL, this may lead to more significant mineralocorticoid effects (Ploeger et al 2001). In order to minimise the risk of side effects, practitioners often use a deglycyrrhizinised form of licorice (DGL).

While *G. glabra*, *G. uralensis* and *G. inflata* are often seen as similar remedies, there are some differences in the constituents, such as the phenolic contents (Mills & Bone 2000).

standardisation of herbs such as licorice provides a challenge for demonstrating reproducible efficacy in clinical settings.

MAIN ACTIONS

Mineralocorticoid effect

The GA constituent in licorice (and its metabolite 3-monoglucuronyl-glycyrrhetinic acid) inhibits the enzyme 11HSD (Kato et al 1995), which catalyses the conversion of cortisol into its inactive metabolite, cortisone. This results in delayed excretion and prolonged activity of cortisol. Additionally, GL and GA bind to mineralocorticoid and glucocorticoid receptors and may displace cortisol from its carrier molecule, transcortin (Nissen 2003).

Pseudohyperaldosteronism

As cortisol levels rise, they stimulate mineralocorticoid receptors in the distal renal tubule (Walker et al 1992). This creates pseudohyperaldosteronism, which has the same clinical features as primary aldosteronism, including sodium retention, fluid retention and oedema, hypertension, hypokalaemia and metabolic alkalosis (Armanini et al 1996, Heldal & Midtvedt 2002, Kato et al 1995, vanUum et al 1998, Walker & Edwards 1994).

A case report suggests that the symptoms occur despite low plasma levels of aldosterone (Nobata et al 2001). Decreased plasma renin activity (Bernardi et al 1994, Epstein et al 1977) and increased cortisol levels result in vasoconstriction of vascular smooth muscle (Dobbins & Saul 2000, Walker et al 1992), which may further exacerbate the hypertensive effects. This may be of particular significance in patients with prolonged intestinal transit time where GA levels can accumulate (Ploeger et al 2001).

Anti-inflammatory

The anti-inflammatory action of beta-glycyrrhetinic acid (GA), a major metabolite of GL, is largely mediated by cortisol, an endogenous hormone with anti-inflammatory action (Teelucksingh et al 1990). It inhibits glucocorticoid metabolism and therefore potentiates its effects.

Several studies have found that GA inhibits the activity of 11HSD and hepatic delta-4-5-beta-steroid reductase, preventing the conversion of cortisol to its inactive metabolite, cortisone (Kageyama et al 1997, MacKenzie et al 1990, Soma et al 1994, Whorwood et al 1993). As such, cortisol activity is prolonged and levels may rise, thereby increasing its anti-inflammatory effects. It may also inhibit classical complement pathway activation (Asl & Hosseinzadeh 2008). For these reasons, licorice has also been investigated for its ability to potentiate the effects of steroid medications (Teelucksingh et al 1990).

This mechanism alone does not fully account for the anti-inflammatory effects of licorice as oral doses of GL also appear to exert an effect in adrenalectomised rats (Gujral et al 2000). GL (10 mg/kg i.p. 5 min prior to carrageenan) exerts potent anti-inflammatory effects in mice by preventing the activation of nuclear factor (NF)-kappaB and STAT-3 (Menegazzi et al 2008). The DGL also exerts anti-inflammatory effects and steroid-like activity has also been attributed to the liquiritin constituent (Bradley 1992).

Anti-allergic

The anti-allergic effects of licorice are mainly due to GL, 18-beta-glycyrrhetinic acid and liquiritigenin, which can relieve IgE-induced allergic reactions, inhibit passive cutaneous anaphylactic reactions and scratching behaviour in mice (Shin et al 2007). A mouse model of asthma GL (5 mg/kg) markedly inhibited airway constriction and hyperreactivity, lung inflammation and infiltration of eosinophils in the peribronchial and perivascular areas. It decreased interleukin (IL)-4, IL-5 and ovalbumin-specific IgE levels (Ram et al 2006). These effects may prove beneficial for the treatment of allergic conditions such as asthma and dermatitis; however, further research is required.

Mucoprotective

Early investigation into the mucoprotective qualities of licorice led to the development of the anti-inflammatory and anti-ulcer medications, carbenoxolone (a hemisuccinate derivative of GA), and enoxolone (an analogue of carbenoxolone) used to treat gastric and oesophageal ulcer disease. Researchers have suggested that it may exert its mucoprotective effects by increasing mucosal blood flow as well as mucus production, and by interfering with gastric prostanoid synthesis (Guslandi 1985). Animal studies indicate that licorice preparations such as DGL improve the environment in the stomach by increasing mucus production, thereby allowing for proliferation of tissue and healing to occur. DGL increases mucus production by increasing the number of fundus glands and the number of mucus-secreting cells on each gland (van Marle et al 1981).

The increase in mucus production seen with carbenoxolone and licorice appears to occur in a number of epithelial tissues other than the digestive tract. It has been reported in the lungs and also bladder, according to in vivo studies (Mooreville & Fritz 1983), and in the trachea, accounting for its expectorant properties (Bradley 1992).

Anti-ulcer effects

Licorice demonstrates the ability to promote mucosal repair and reduce symptoms of active ulcer (Larkworthy & Holgate 1975).

The anti-ulcer effects of licorice are due to inhibition of 15-hydroxyprostaglandin dehydrogenase (which converts prostaglandin E2 (PGE_2) and F_{2alpha} to their inactive forms) and delta-13-PG reductase. Licorice-derived compounds therefore increase the local concentration of PGs that promote mucus secretion and cell proliferation in the stomach, leading to healing of ulcers (Baker 1994).

Anti-inflammatory activity (as described above) further contributes to the herb's symptom-relieving action.

Antiviral

Both oral and injectable dose forms of licorice have been tested and found to have activity against a range of viruses. In human trials, GL and its derivatives reduce the liver sequelae associated with hepatitis B and C viruses; animal studies demonstrate a reduction in viral activity for herpes simplex virus, encephalitis and influenza A virus pneumonia; and in vitro studies reveal antiviral activity against HIV-1, severe acute respiratory syndrome (SARS) related coronavirus, respiratory syncytial virus, arboviruses, vaccinia virus and vesicular stomatitis virus (Fiore et al 2008). The effects appear to be mediated by the constituents GL and GA (Jeong & Kim 2002). The proposed mechanisms for these antiviral effects include 'reduced transport to the membrane and sialylation of hepatitis B virus surface antigen, reduction of membrane fluidity leading to inhibition of fusion of the viral membrane of HIV-1 with the cell, induction of interferon gamma in T-cells, inhibition of phosphorylating enzymes in vesicular stomatitis virus infection and reduction of viral latency' (Fiore et al 2008). It should be noted that current studies focus largely on GL, which is converted in the gut to GA and may not produce the same results as those demonstrated for GL in vitro.

SARS-associated coronavirus

In vitro studies have shown GL to inhibit SARS-CV (clinical isolates FFM-1 and FFM-2) replication by inhibiting adsorption and penetration of the virus in the early steps of the replicative cycle. GL was most effective when given both during and after the adsorption period. High concentrations of GL (4000 mg/L) were found to completely block replication of the virus (Cinatl et al 2003). The ability of GL to reduce platelet accumulation in the lungs (Yu et al 2005) may also support this use and provide a possible therapeutic option for further investigation.

HIV

Preliminary evidence indicates that intravenous administration of GL may reduce replication of HIV. High-dose GL (1600 mg/day) was most effective in reducing HIV type 1 p24 antigen and increasing lymphocytes (Hattori et al 1989). In vitro, GL has the potential to inhibit viral replication in cultures of peripheral blood mononuclear cells from HIV-infected patients infected with a non-syncytium-inducing variant of HIV (Sasaki et al 2002–03).

Influenza

Animal studies have shown that GL offers protection against influenza virus in mice through stimulation of interferon-gamma production by T-cells (Utsunomiya et al 1997).

Epstein–Barr virus

In vitro studies suggest that GL may interfere with an early step of the Epstein Barr Virus replication cycle (possibly penetration) (Lin 2003).

Herpes simplex virus 1

In Kaposi sarcoma-associated herpes virus (KSHV), GL reduced the synthesis of a viral latency protein and induced apoptosis of infected cells (Cohen 2005) terminating KSHV latent infection of B-lymphocytes (Bradbury 2005). Early in vitro studies found that GL inactivated Herpes Simplex Virus irreversibly (Pompei et al 1979). Animal studies show that intraperitoneal administration of GL reduces HSV-1 viral replication and improves survival from herpetic encephalitis in mice (Sekizawa et al 2001). Whether GL may act against other latent herpes viruses or be suitable for clinical use against KSHV requires further elucidation (Bradbury 2005).

Antibacterial

A number of constituents in licorice, including phenolic compounds (glicophenone and glicoisoflavanone), licochalcone A and isoflavones, were found to have antibacterial effects on Methicillin-Resistant *Staphylococcus aureus* and Methicillin-Sensitive *Staphylococcus aureus* in vitro (Hatano et al 2000). Glabridin has been identified as a potentially active agent against *Mycobacterium tuberculosis* (H(37)Ra and H(37)Rv strains), gram-positive and gram-negative bacteria (Gupta et al 2008). Additionally ether–water extracts of licorice have been found to have antibacterial activity against *E. coli*, *B. subtilis*, *E. aerogenes*, *K. pneumoniae* and *S. aureus* (Onkarappa et al 2005).

Expectorant

Expectorant effects may be attributed to the ability of licorice to stimulate tracheal mucus secretion, facilitating the elimination of mucus from the respiratory tract (Bradley 1992).

Antitussive

In animal studies licorice produces a persistent antitussive effect, which is mediated by liquiritin apioside in the earlier phase and liquiritin and liquiritigenin (a metabolite of liquiritin apioside) in the later phase (Kamei et al 2005). Isoliquiritigenin has also been shown to induce tracheal relaxation in guinea pig models (Liu et al 2008).

Antioxidant

In vitro research has identified seven antioxidant compounds from an acetone extract of licorice: four isoflavans (hispaglabridin A, hispaglabridin B, glabridin and 4′-*O*-methylglabridin), two chalcones (isoprenylchalcone derivative and isoliquiritigenin) and an isoflavone (formononetin) (Vaya et al 1997). Isoflavones from licorice were also shown to be effective in protecting mitochondrial function against oxidative stresses (Haraguchi 2000).

Reduces lipid peroxidation

Macrophage-mediated oxidation of LDL cholesterol plays a major role in early atherogenesis. In animal models, glabridin accumulates in macrophages and inhibits macrophage-mediated oxidation of LDL by up to 80% (Aviram 2004). DGL (100 mg/day for 2 weeks) was found to reduce lipid peroxidation of

LDL cholesterol after 1 week's use according to a placebo-controlled trial (Fuhrman et al 1997).

Lipid lowering

Administration of licorice root powder (5 and 10 g in diet) to hypercholesterolaemic male albino rats for 4 weeks resulted in a 'significant reduction in plasma, hepatic total lipids, cholesterol, triglycerides and plasma low-density lipoprotein and VLDL cholesterol accompanied by significant increases in HDL cholesterol levels'. These effects may have been due in part to increases in faecal cholesterol, neutral sterols and bile acid excretion and an increase in hepatic 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase activity and bile acid production. Additionally, decreased hepatic lipid peroxidation with a concomitant increase in superoxide dismutase (SOD) and catalase activities and total ascorbic acid content were noted. In normocholesterolaemic rats, the higher dose also led to a significant reduction in plasma lipid profiles and an increase in HDL cholesterol content (Visavadiya & Narasimhacharya 2006).

Anticancer effects

Licorice has demonstrated potent anti-angiogenic and antitumour activity in animal studies (Sheela et al 2006). Animal and in vitro studies have shown licorice components to be effective in reducing the occurrence and number of tumour cells in several cancer models (Shibata 1994, Wang & Mukhtar 1994, Wang & Nixon 2001), inducing apoptosis and potentiating the effect of paclitaxel and vinblastine chemotherapy (Rafi et al 2000). In vitro research reveals that chalcone and isoliquiritigenin significantly inhibit the proliferation of prostate cancer cell lines in a dose- and time-dependent manner and that beta-hydroxy-DHP inhibits breast and prostate tumour cells (Kanazawa et al 2003, Maggiolini et al 2002, Rafi et al 2002). Isoliquiritigenin has also been shown to significantly inhibit the proliferation of lung and colon cancer cells, restrain cell cycle progression and induce apoptosis (Chin et al 2007, Ii et al 2004, Takahashi et al 2004).

Although the exact mechanism of action is still being determined, a 2001 review indicates that licorice and its derivatives may protect against carcinogen-induced DNA damage and that GA is an inhibitor of lipo-oxygenase and cyclo-oxygenase, inhibits protein kinase C, and down-regulates the epidermal growth factor receptor (Wang & Nixon 2001).

Cognitive function

Glycyrrhiza glabra has shown promise as a memory-enhancing agent in both exteroceptive and interoceptive behavioural models of memory in mice. The effect is possibly due to facilitation of cholinergic transmission in the mouse brain (Dhingra et al 2004, Parle et al 2004). In animal models, glabridin appears to reduce brain cholinesterase activity in mice (Cui et al 2008). In rats significant spatial memory retention enhancement has also been observed after 4 weeks of licorice administration (aqueous extract equivalent to 5 mg/mL of GL) in drinking water (Sharifzadeh et al 2008).

Neuroprotective

GL has also been shown to reduce the development of inflammation and tissue injury associated with spinal cord trauma in mice resulting in improved recovery of limb function (Genovese et al 2008). Several other constituents have also demonstrated possible neuroprotective effects. Glabridin (25 mg/kg by intraperitoneal injection) was able to modulate the cerebral injuries induced by middle cerebral artery occlusion (MCAO) in rats. The neuroprotective effect appeared to be at least in part associated with the modulation of multiple pathways associated with apoptosis (Yu et al 2008). In addition, pretreatment with isoliquiritigenin (5, 10 and 20 mg/kg, i.g.) significantly reduced cerebral infarct volume and oedema, and produced a significant reduction in neurological deficits due to MCAO-induced focal cerebral ischaemia-reperfusion injury in rats (Zhan & Yang 2006).

Antidepressant (serotonin reuptake inhibition)

Several flavonoid constituents in licorice (glabridin 60%, 4′-*O*-methylglabridin 53% and glabrene 47%) inhibit serotonin reuptake in a dose-dependent manner, according to in vitro research (Ofir et al 2003). However, animal models suggest that the effect may be on noradrenaline and dopamine. In rats licorice extract (150 mg/kg) administered orally for 7 days exerted an antidepressant effect comparable to that of imipramine (15 mg/kg i.p.) and fluoxetine (20 mg/kg i.p.), the effect however appeared to be mediated by an increase of brain noradrenaline and dopamine, not serotonin. It is likely that licorice exerts a monoamine oxidase inhibiting effect (Dhingra & Sharma 2006).

Hepatoprotective effects

Randomised controlled trials have confirmed that GL and its derivatives reduce hepatocellular damage in chronic hepatitis B and C and reduce cirrhosis and hepatocellular carcinoma risk in hepatitis C (Fiore et al 2008). Animal studies demonstrate that licorice protects hepatocytes by inhibiting experimentally induced lipid peroxidation (Rajesh & Latha 2004). GL appears to alleviate carbon tetrachloride-induced liver injury by inducing haem oxygenase-1 and down-regulating pro-inflammatory mediators (tissue necrosis factor (TNF)-alpha, inducible nitric oxide synthase, and cyclo-oxygenase-2 mRNA expression) (Lee et al 2007). In vitro studies have shown hepatoprotective effects of GL against aflatoxin B1-induced cytotoxicity in human hepatoma cells (Chan et al 2003) and animal studies have shown GA exerts hepatoprotective effects against carbon tetrachloride-induced liver injury (Jeong et al 2002).

Several mechanisms appear to be responsible for the hepatoprotective effect. Glycyrrhizic acid enhances the detoxifying activity of the liver enzyme CYP1A1 and glutathione S-transferase and protects against oxidative stress, when induced by aflatoxin (Chan et al 2003).

Animal studies have found that GA inhibits expression of the liver enzyme CYP2E1. Once again, antioxidant mechanisms appear to be involved, as GA prevented glutathione depletion, an increase in ALT, AST activity, and hepatic lipid

peroxidation in a dose-dependent manner when carbon tetrachloride exposure occurred (Jeong et al 2002). In addition, isoliquiritigenin may stimulate the proliferation of human hepatocytes according to in vitro studies (De Bartolo et al 2005).

Antiplatelet effect

Isoliquiritigenin purified from licorice has been shown to inhibit platelet aggregation in vitro and in vivo (Francischetti et al 1997, Kimura et al 1993, Tawata et al 1992). Whether the effect is clinically significant for licorice remains to be determined. Newer data indicate that GL is an effective thrombin inhibitor in vivo (Mendes–Silva et al 2003).

OTHER ACTIONS

Sex hormones

Testosterone

Whether licorice consumption affects testosterone levels is still unknown, as conflicting results have been obtained from clinical studies. Armanini et al have conducted a series of trials investigating the effects of licorice on testosterone levels in males with mixed results (Armanini et al 1999, 2003a).

One study showed that licorice (7 g/day equivalent to 0.5 g GA) was able to reversibly reduce testosterone levels within 7 days, by inhibiting 17,20-lyase (involved in the conversion of 17-hydroxyprogesterone to androstenedione) and 17-beta-hydroxysteroid dehydrogenase (involved in the conversion of androstenedione to testosterone) (Armanini et al 1999). Another study twice attempted to replicate these results, but was unable to detect an effect on testosterone levels in either study; the authors suggest that inappropriate use of statistical tests in the first study may explain the varying results (Josephs et al 2001).

More clinically promising are the results from a small trial of nine healthy women (22–26 years) in the luteal phase of their menstrual cycle. The women received 3.5 g licorice (containing 7.6% w/w of GL) daily for two cycles. Total serum testosterone decreased from 27.8 (±8.2) to 19.0 (±9.4) ng/dL in the first month and to 17 (±6.4) ng/dL in the second month of therapy (Armanini et al 2004). Further larger scale trials are required to confirm these effects in women with conditions of elevated testosterone such as hirsutism and polycystic ovary syndrome (PCOS).

Oestrogen

Licorice contains isoflavones, including licochalcone A, which are also known as 'phyto-oestrogens' because they act as partial oestrogen agonists in the body (Setchell & Cassidy 1999). Additionally, in vitro studies suggest that stimulation of aromatase activity promotes oestradiol synthesis (Takeuchi et al 1991).

Liquiritigenin and isoliquiritigenin have displayed oestrogenic affinity to sex hormone-binding globulin and oestrogen receptors in vitro (Hillerns et al 2005) and glabridin and glabrene have both demonstrated oestrogen-like activities similar to oestradiol-17(beta) in animal studies (Somjen et al 2004a).

In vitro studies also suggest the potential for glabridin to enhance osteoblast function (Choi 2005). As a result glabridin has been proposed as a possible therapeutic aid in the prevention of osteoporosis and inflammatory bone diseases (Choi 2005), as well as cardiovascular diseases and bone disorders, in postmenopausal women (Somjen et al 2004a, 2004b).

Immunomodulation

Although immunostimulating effects have been observed in experimental models (Lin et al 1996), elevated cortisol levels, which are also induced by licorice, may theoretically reduce this effect (Padgett & Glaser 2003).

Inhibition of aldolase reductase

In vitro studies show that licorice may suppress sorbitol accumulation in red blood cells by inhibiting aldolase reductase (Zhou & Zhang 1990). The isoliquiritigenin component appears to be responsible (Aida et al 1990a). This may have positive implications in diabetes.

CLINICAL USE

Peptic ulcer and dyspepsia

The anti-inflammatory, mucoprotective and anti-ulcer activities of licorice make it an attractive treatment for peptic ulcer. While these effects have been attributed to the GL and GA constituents, the DGL, which contains < 3% GL, has also been investigated and appears to produce the most promising results when used long term (Bardhan et al 1978, Larkworthy & Holgate 1975). DGL also promotes differentiation of undifferentiated cells to mucous cells and stimulates mucus production and secretion (van Marle et al 1981).

In an uncontrolled trial of 32 patients with chronic duodenal ulcer, 3800 mg/day of DGL (in five divided doses) produced signs of healing in all cases and total restoration of mucosa in a majority of subjects. Although treatment continued for 24 weeks, considerable improvement was seen in 56% of patients by week 12 and in 78% by week 16 (Larkworthy & Holgate 1975). A shorter 4-week trial of 96 patients with gastric ulcer failed to produce the same positive results (Bardhan et al 1978).

DGL plus antacid (Caved-S; two tablets chewed three times daily between meals) was as effective as cimetidine (200 mg three times daily plus 400 mg at night) after 6 weeks, according to one randomised single-blind trial of 100 volunteers with peptic ulcer. The two treatments continued to produce similar results after 12 weeks and recurrence rates after both medications were reduced were also similar (Morgan et al 1982).

Commission E approves the use of licorice for the treatment of gastric and duodenal ulcers (Blumenthal et al 2000).

Dermatitis

The anti-inflammatory effect induced by GA provides a theoretical basis for its use as a topical anti-inflammatory agent (much like hydrocortisone) in the treatment of dermatitis.

In practice, GA has been used to potentiate the effects of weak steroids (such as hydrocortisone) in order to increase pharmacological effects without the need for stronger corticosteroids (Teelucksingh et al 1990). It is assumed that increasing corticosteroid activity in this way will not attract an increase in adverse effects; however, no studies have yet confirmed this.

An early study comparing the effects of hydrocortisone- and GA-containing ointments in dermatitis found that hydrocortisone was usually superior in acute and infantile eczemas, whereas GA was superior for chronic and subacute conditions (Evans 1958).

It should be noted that GA is many times more powerful inhibitor of 11HSD than GL and therefore should theoretically induce far stronger anti-inflammatory effects. GA is not present in licorice but is produced in the gastrointestinal tract from GL; therefore, it is uncertain whether topical preparations containing pure licorice are likely to produce significant anti-inflammatory effects.

Allergic conditions

The anti-allergic effects of licorice (Ram et al 2006, Shin et al 2007) provide a theoretical basis for the treatment of allergic conditions such as asthma and dermatitis; however, further research is required.

Viral infections

In human trials, GL and its derivatives reduce the liver sequelae associated with hepatitis B and C viruses; animal studies demonstrate a reduction in viral activity for herpes simplex virus, encephalitis and influenza A virus pneumonia; and in vitro studies reveal antiviral activity against HIV-1, SARS related coronavirus, respiratory syncytial virus, arboviruses, vaccinia virus and vesicular stomatitis virus (Fiore et al 2008). However, until controlled studies are available, the clinical effectiveness of this treatment remains unknown.

Respiratory tract infections

Licorice increases mucus production within the respiratory tract and exerts an expectorant (Bradley 1992) and antitussive effect (Kamei et al 2005). When combined with its anti-inflammatory, antiviral and possible immune-enhancing effects, it is a popular treatment for upper and lower respiratory tract infections. In practice, it is often used to treat coughs (especially productive types) and bronchitis (Bradley 1992).

Commission E approves the use of licorice for catarrhs of the upper respiratory tract (Blumenthal et al 2000).

Chronic stress

Traditionally, licorice is viewed as an 'adrenal tonic', most likely due to its ability to slow cortisol breakdown. It may be of benefit in patients experiencing allostatic load due to chronic stress and who are therefore unable to mount a healthy stress response. This is also known as adrenocorticoid insufficiency. Controlled trials are not available to determine its effectiveness in this situation.

Whether this effect is desirable in patients without adrenocorticoid insufficiency and for whom increased cortisol levels may prove problematic is open to conjecture. Chronically high cortisol levels have been associated with desensitisation of the hypothalamic-pituitary-adrenal (HPA) axis, insulin resistance, depression and immunosuppression (Blackburn-Munroe 2001, Jessop 1999, Mitchell & Mitchell 2003). In the initial stages of stress, increased cortisol levels trigger negative feedback mechanisms to keep stress under control and, therefore, short-term use may be warranted but is unlikely to be beneficial unless some adrenocorticoid insufficiency exists.

(For more information see 'Clinical note — Allostasis' in the Siberian ginseng monograph.)

OTHER USES

Licorice has also been used traditionally as a sweetener and aromatic flavouring agent.

Although controlled trials are lacking, licorice is also used for a number of other conditions, largely based on evidence of pharmacological activity.

Chronic fatigue syndrome

The ability of licorice to slow cortisol catabolism may provide a theoretical basis for its use in cases of chronic fatigue syndrome (CFS) accompanied by low cortisol levels. A case report exists of a patient experiencing improved physical and mental stamina and recovery from CFS following use of licorice dissolved in milk (2.5 g/500 mL/day) (Baschetti 1995, 1996).

Polycystic ovary disease

The possibility that licorice may lower testosterone levels in women provides a theoretical basis for its use in PCOS (Armanini et al 2004). While trials using licorice as a stand-alone treatment are lacking, studies of licorice in combination with other herbal medicines such as peony have produced promising results, showing reductions in LH:FSH ratio, ovarian testosterone production and improvements in ovulation (Takahashi & Kitao 1994, Takahashi et al 1988).

Preventing diabetic complications

In diabetic patients with neuropathy, retinopathy or nephropathy, sorbitol:glucose ratios are significantly higher than in those without these complications and ratios increase as complications become more severe (Aida et al 1990b). As licorice and its component isoliquiritigenin have been shown to inhibit aldolase reductase and suppress sorbitol accumulation in red blood cells in vitro (Aida et al 1990b, Zhou & Zhang 1990), a theoretical basis exists for its use in the prevention of diabetic complications.

Menopause

Inhibition of serotonin reuptake and possible oestrogenic activity provide a theoretical basis for its use in pre- and postmenopausal women with mild to moderate depression (Ofir et al 2003, Takeuchi et al 1991).

Constituents in licorice may bind to oestrogen receptors, enhance osteoblast function and attenuate vascular injury and atherosclerosis (Choi 2005; Somjen et al 2004a, 2004b) suggesting a possible role in the prevention of bone disorders and cardiovascular diseases in postmenopausal women.

Weight loss

The action of GA in blocking 11HSD type 1 at the level of fat cells may help to explain preliminary evidence suggesting an ability to reduce body fat mass and the thickness of thigh fat (Armanini et al 2003b, 2005).

Addison's disease

The ability of licorice to reduce cortisol breakdown provides a theoretical basis for its use in Addison's disease, either as a stand-alone treatment, when adrenocortical function is not severely impaired, or as an adjunct to cortisone therapy. While studies in the 1950s confirm this use (Borst et al 1953, Calvert 1954, Pelser et al 1953), recent studies are not available. A case report exists of an 11-year-old boy with hypoparathyroidism and Addison's disease developing hypermineralocorticoidism following excessive intake of licorice (300–400 g/day, equivalent to 600–800 mg GL) concurrently with hydrocortisone and 9-alpha-fluorocortisol. Pseudohyperaldosteronism persisted after treatment with 9-alpha-fluorocortisol was withdrawn and hydrocortisone was reduced; however, symptoms only diminished after the complete withdrawal of licorice. It was suggested that inhibition of 11HSD by licorice was responsible due to increased levels of free cortisol (Doeker & Andler 1999).

Hypercholesterolaemia

Preliminary studies in rats suggest a possible role for licorice root powder in the treatment of hypercholesterolaemia; however, clinical trials in humans need to be conducted to investigate this effect (Visavadiya & Narasimhacharya 2006).

Depression

Licorice extract (150 mg/kg) appears to exert a monoamine oxidase inhibiting effect in rats, increasing brain noradrenaline and dopamine, and resulting in an antidepressant effect comparable to that of imipramine (15 mg/kg i.p.) and fluoxetine (20 mg/kg i.p.) (Dhingra & Sharma 2006). Further studies are required to elucidate these effects in humans.

DOSAGE RANGE

- Fluid extract (1:1): 2–4 mL three times daily or 15–40 mL/week (Australian manufacturer recommendations).
- Root: 5–15 g/day (equivalent to 200–600 mg of GL).
- Tea: pour 150 mL boiling water over one teaspoon (2–4 g) licorice root, simmer for 5 minutes and filter through a tea strainer after cooling.
- Chronic gastritis: one cup of licorice tea after each meal.

According to clinical studies

- Chronic duodenal ulcers: 3800 mg/day of DGL (in five divided doses) before meals and at bedtime.
- Ideally, licorice extracts should contain > 30 mg/mL GL.

ADVERSE REACTIONS

Many of the adverse effects attributed to licorice are due to GA at doses above 100–400 mg/day. For this reason, the DGL may be safer and more appropriate in cases where GL or GA is not required for efficacy.

Side effects may be more pronounced in people with essential hypertension who appear to be more sensitive to the inhibition of 11HSD by licorice than normotensive subjects (Sigurjonsdottir et al 2003).

- Hypercortisolism and pseudohyperaldosteronism — associated with sodium retention, potassium loss and suppression of the renin–angiotensin–aldosterone system and presenting as hypertension, fluid retention, breathlessness, hypernatraemia and hypokalaemia (Bernardi et al 1994, Blachley & Knochel 1980, Dellow et al 1999, Kageyama et al 1997, Wash & Bernard 1975).
- Hypokalaemia — may present as hypotonia and flaccid paralysis, peripheral oedema, polyuria, proximal myopathy, lethargy, paraesthesiae, muscle cramps, headaches, tetany, breathlessness and hypertension (deKlerk et al 1997, Eriksson et al 1999). In practice, licorice is often mixed with the potassium-rich herb dandelion leaf, which also has mild diuretic effects.
- Hypokalaemic paralysis — although rare, some cases have been reported as a result of chronic licorice use (Corsi et al 1983, Lin et al 2003, Shintani et al 1992, van-den-Bosch et al 2005). A case report of a young female presenting with acute onset quadriparesis secondary to severe hypokalaemia has been attributed to a polyherbal preparation containing licorice (Mukherjee et al 2006).
- Rhabdomyolysis — a number of cases are reported in the scientific literature (Firenzuoli & Gori 2002, van-den-Bosch et al 2005) as a result of severe hypokalaemia.
- Dropped head syndrome — a case report exists of dropped head syndrome (isolated weakness of the extensor muscles of the neck) due to licorice-induced hypokalaemia (Yoshida & Takayama 2003).
- Hypertension encephalopathy may occur even at low doses in susceptible patients with 11-beta-HSD deficiency (Russo et al 2000).
- Reduced 11-beta-HSD activity may have a role in increased sodium retention in pre-eclampsia, renal disease and liver cirrhosis. Reduced placental levels may explain the link between reduced birth weight and adult hypertension (the Barker hypothesis) (Quinkler & Stewart 2003).
- Juvenile hypertension — inhibition of 11HSD may also contribute to a rare form of juvenile hypertension (Chamberlain & Abolnik 1997, White et al 1997).
- Visual disturbance — ingestion of high doses of licorice (110–900 g) has been reported to elicit symptoms of visual disturbance in a case series of

five patients. This may be attributed to the possible ability of licorice to 'stimulate retinal and occipital vasospasm and vasospasm of vessels supplying the optic nerve' (Dobbins & Saul 2000).

SIGNIFICANT INTERACTIONS

Controlled trials exist that have identified drug interactions. However, in most cases, the interactions are based on evidence of pharmacological activity, case reports or theoretical reasoning. The DGL form is considered safer and less likely to result in drug interactions.

Glabridin is a substrate of P-glycoprotein (P-gp/MDR1) (Cao et al 2007); therefore, potential drug–glabridin interactions need to be considered until more clinical data are available (Yu et al 2007).

Acetylsalicylic acid and other gastro-irritant anti-inflammatory drugs

Co-administration with licorice may reduce gastro-irritant effects induced by drug therapy — potentially beneficial interaction. 1993, Tawata et al 1992). Whether the effect is clinically significant for licorice remains to be determined — use high doses with caution.

Antihypertensives

High-dose GL taken long term can lead to increased blood pressure, thereby reducing drug efficacy. Caution — monitor blood pressure when high-dose licorice preparations are taken for longer than 2 weeks.

Chemotherapy (paclitaxel and vinblastine)

A constituent of licorice has demonstrated significant potentiation of paclitaxel and vinblastine chemotherapy in vitro (Rafi et al 2000). Observe.

Cimetidine and other H2 antagonists

Adjunctive licorice treatment may enhance ulcer-healing drug effects — potentially beneficial interaction.

Corticosteroids

Concurrent use of licorice preparations potentiates the effects of topical and oral corticosteroids (e.g. prednisolone). Some practitioners employ licorice to minimise requirements for or aid in withdrawal from corticosteroid medications. Beneficial interaction is possible under professional supervision, but patients may require a reduction in corticosteroid dosage to avoid corticosteroid excess (Chen et al 1991, Homma et al 1994).

Diclofenac sodium (NSAID)

In vitro studies have shown that the addition of GL enhanced the topical absorption of diclofenac sodium (Nokhodchi et al 2002), which may be a beneficial interaction.

Digoxin

Hypokalaemia increases sensitivity to cardiac glycoside drugs, therefore increased digoxin toxicity is possible when licorice is used in high doses for more than 2 weeks. A case report exists of congestive heart failure caused by digitalis toxicity in an elderly man taking a licorice-containing Chinese herbal laxative (Harada et al 2002). Avoid long-term use of high-dose licorice preparations and digoxin concurrently.

Diuretics (including loop, thiazide and potassium-depleting)

Case reports exist in which patients experience hypokalaemia and hypertension with concomitant use of licorice and diuretics (deKlerk et al 1997, Farese et al 1991, Folkerson et al 1996) due to increased potassium excretion. Avoid long-term use of licorice and diuretics concurrently unless under professional supervision — monitor potassium levels.

Oral contraceptive pill

An increased risk of side effects such as hypokalaemia, fluid retention and elevated blood pressure due to increased mineralocorticoid effect exists. This has been demonstrated in case reports (Bernardi et al 1994, deKlerk et al 1997). Use this combination with caution when licorice is used in high dose or for more than 2 weeks and observe patients closely.

Potassium

Licorice may reduce the effect of potassium supplementation. A case report exists of a 69-year-old female developing hypokalaemia while taking potassium supplements and a mouth freshener containing licorice concurrently. The daily intake of GA was estimated at 6–10 mg/day (Kageyama et al 1997). In many cases potassium supplementation may be beneficial in reducing the hypokalaemic side effects of licorice.

Testosterone

Licorice may decrease testosterone levels, although clinical tests have produced conflicting results (Armanini et al 1999, 2003a, 2004, Sakamoto & Wakabayashi 1988, Takeuchi et al 1991) — observe and monitor patients for reduced testosterone effects.

Drugs metabolised by liver enzymes CYP3A4, 2B6, 2C9, 2E1 or 1A1

Licorice inhibits CYP3A4 in vitro (Budzinski et al 2000), the glabridin constituent inhibits CYP2B6, 2C9 and 3A4 in vitro (Kent et al 2002), GA inhibits its expression of CYP2E1 in animal studies (Jeong et al 2002) and GL enhances the detoxifying activity of CYP1A1 (Chan et al 2003). Until testing in humans can establish whether the effects are clinically significant and relevant to licorice in therapeutic doses, caution is advised if licorice is administered with drugs chiefly metabolised by these enzymes. (See chapter on Interactions for more information.)

CONTRAINDICATIONS AND PRECAUTIONS

Licorice should be used with caution in people with hypertension (or a genetic predisposition to hypertension) or fluid retention, and is contraindicated

in hypotonia, severe renal insufficiency, hypokalaemia, liver cirrhosis and cholestatic liver disease (Blumenthal et al 2000). The effects are likely to be dose dependent and more likely in people with essential hypertension with a particular tendency to 11HSD inhibition by licorice (Sigurjonsdottir et al 2001, 2003). It is also contraindicated in people with a deficiency in 11HSD (Russo et al 2000).

Long-term use (> 2 weeks) at therapeutic doses should be monitored closely due to the potential side effects. Additionally, a high-potassium low-sodium diet should be consumed during treatment (Bradley 1992, McGuffin et al 1997).

As licorice may questionably reduce testosterone levels in men, it should be used with caution in men with a history of impotence, infertility or decreased libido (Armanini et al 1999, Zava et al 1998).

PREGNANCY USE

Licorice is contraindicated in pregnancy. A Finnish trial found that high consumption of licorice during pregnancy increased the likelihood of early delivery but did not significantly affect birth weight or maternal blood pressure (Strandberg et al 2001).

PRACTICE POINTS/PATIENT COUNSELLING

- Licorice has been used as a food, flavouring agent and medicine since ancient times.
- It exhibits mineralocorticoid, anti-inflammatory, antioxidant, mucoprotective and ulcer-healing activity in humans. Antiviral, antibacterial, antitumour, expectorant and hepatoprotective effects have also been demonstrated in animal or test tube studies. Significant effects on oestrogen and testosterone levels remain to be established in controlled trials as evidence is inconsistent.
- Licorice is a popular treatment for respiratory tract infections, gastrointestinal ulcers and dyspepsia. It is also used to treat chronic stress and numerous other conditions, largely based on evidence of pharmacological activity.
- GA has been used topically as an anti-inflammatory agent and also together with cortisone preparations to increase effects.
- High-dose licorice (> 100 mg GL) used for more than 2 weeks can induce hypokalaemia and pseudoaldosteronism in susceptible individuals. As such, it should be used with caution and under professional supervision. Additionally, it interacts with numerous medicines. The DGL form is considered safer.

PATIENTS' FAQs

What will this herb do for me?

Licorice has many effects in the body, the most well-established ones being reducing inflammation, enhancing healing of peptic ulcers and treating infections such as bronchitis and cough.

When will it start to work?

Beneficial effects in peptic ulcer occur within 6–12 weeks, although DGL is usually used to avoid side effects. Symptoms of dyspepsia should respond within the first few doses. Effects in bronchitis will vary between individuals.

Are there any safety issues?

Used in high doses for more than 2 weeks, licorice can induce several side effects such as raised blood pressure and fluid retention and may interact with a number of drugs. The DGL form is considered safer.

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Lutein and zeaxanthin

BACKGROUND AND RELEVANT PHARMACOKINETICS

Lutein and its isomer, zeaxanthin, are yellow-coloured, xanthophyll carotenoids that are not converted into vitamin A. The bioavailability of lutein and zeaxanthin from food sources is influenced by the food matrix and by the type and extent of food processing, but most notably by the presence of fat in the diet (Castenmiller et al 1999), with dietary fat intake being inversely related to serum levels (Nolan et al 2004). Cooking may increase their bioavailability by disrupting the cellular matrix and protein complexes, and supplemental sources may be significantly more bioavailable than food sources (Castenmiller et al 1999). It has also been observed that plasma responses to cholesterol and carotenoids are related (Clark et al 2006) and that the bioavailability of zeaxanthin from freeze-dried wolfberries is enhanced 3-fold when consumed in hot skimmed milk compared to hot water or warm milk (Benzie et al 2006). One clinical study found that plasma lutein was higher when lutein was consumed with a high-fat spread (207% increase) than with a low-fat spread (88% increase) (Roodenburg et al 2000). This was supported by a small in vitro study showing that dietary lutein is absorbed more efficiently with 24 g of avocado oil or 150 g of avocado fruit (Unlu et al 2005). For each 10% increase in dietary lutein and zeaxanthin, serum levels are seen to increase by 1% (Gruber et al 2004).

When ingested, lutein and zeaxanthin are transported from the intestine to the liver via chylomicrons. They are then transported via LDL and HDL to various parts of the body (Yeum & Russell 2002). Lutein and zeaxanthin are present in the eye, blood serum, skin, cervix, brain, breast and adipose tissue. In the eye, lutein is more prominent at the edges of the retina and in the rods (Bernstein 2001, Bone et al 1997). Lutein appears to undergo some metabolism in the retina to *meso*-zeaxanthin. Zeaxanthin is primarily concentrated in the centre of the retina and the cones, where it is present in concentrations nearly 1000-fold of those found in other tissues, thus giving the macula lutea or yellow spot of the retina its characteristic colour (Krinsky et al 2003). It is suggested, however, that during supplementation with xanthophylls, lutein is predominantly deposited in the fovea, while zeaxanthin deposition appears to cover a wider retinal area (Schalch et al 2007).

Lower serum concentrations of zeaxanthin have been associated with male gender, smoking, younger age, lower non-HDL cholesterol, greater ethanol consumption and higher body mass index (BMI) (Brady et al 1996). Lutein and zeaxanthin, together with other carotenoids, have also been found to be lower in people with chronic cholestatic liver disease, which can be attributed to malabsorption of fat-soluble vitamins, as well as other mechanisms of hepatic release (Floreani et al 2000). In an epidemiological study involving 7059 participants, lower serum lutein and zeaxanthin levels were significantly associated with smoking, heavy drinking, being white, female, or not being physically active, having lower dietary lutein and zeaxanthin, a higher percentage of fat mass, a higher waist–hip ratio, lower serum cholesterol, a higher white blood cell count and high levels of C-reactive protein (Gruber et al 2004).

In a pharmacokinetic study involving 20 healthy volunteers, serum zeaxanthin levels were found to have an effective half-life for accumulation of 5 days and a terminal elimination half-life of around 12 days (Hartmann et al 2004). This was confirmed

by another study that also found that lutein did not affect the concentrations of other carotenoids in healthy volunteers (Thurmann et al 2005). Similarly, high doses (50 mg) of beta-carotene over 5 years were not found to influence serum levels of lutein and zeaxanthin (Mayne et al 1998). It has been suggested that the associations between macula pigment density and serum lutein, serum zeaxanthin and adipose lutein concentrations are stronger in men (Broekmans et al 2002, Johnson et al 2000) and that the processes governing accumulation and/or stabilisation of zeaxanthin in fat tissue are different for males and females (Nolan et al 2004). This is supported by the finding that serum lutein and zeaxanthin concentrations vary with the menstrual cycle, with levels being higher in the late follicular than in the luteal phase (Forman et al 1998).

CHEMICAL COMPONENTS

Lutein and zeaxanthin are isomers and have identical chemical formulas, differing only in the location of a double bond in one of the hydroxyl groups. Lutein is known as beta, epsilon-carotene-3,3′-diol, whereas zeaxanthin is known as all-*trans* beta-carotene-3,3′-diol.

FOOD SOURCES

Foods differ in their relative amounts of lutein and zeaxanthin, with lutein generally being more abundant. Lutein is found in dark green leafy vegetables such as spinach and kale, as well as in sweet corn and egg yolks, whereas zeaxanthin is found in sweet corn, egg yolk, orange peppers (capsicums), persimmons, tangerines, mandarins and oranges.

Lutein and zeaxanthin are primarily extracted from marigold flowers (*Tagetes erecta*) for use in supplements and are available in either free or esterified form. The esters typically contain two fatty acid groups that must be cleaved by pancreatic esterases and their absorption requires higher levels of dietary fat (Roodenburg et al 2000); however, addition of omega-long-chain polyunsaturated fatty acids to oral supplementation of lutein/zeaxanthin has not been found to change serum levels of lutein and zeaxanthin (Huang et al 2008).

DEFICIENCY SIGNS AND SYMPTOMS

It has been suggested that zeaxanthin and lutein be considered conditionally essential nutrients because low serum levels or low dietary intakes are associated with low macular pigment density (Mares et al 2006) and increased risk of age-related macular degeneration (ARMD) (Semba & Dagnelie 2003).

Epidemiological studies have also found an association between low serum carotenoid levels, including lutein and zeaxanthin levels, with all-cause mortality (De Waart et al 2001), the risk of inflammatory polyarthritis (Pattison et al 2005), breast cancer (Tamimi et al 2005), prostate cancer (Jian et al 2005), colon cancer (Nkondjock & Ghadirian 2004), cervical cancer (Garcia-Closas et al 2005, Kim et al 2004), human papilloma virus persistence (Garcia-Closas et al 2005), type 2 diabetes and impaired glucose metabolism (Coyne et al 2005), chronic cholestatic liver diseases (Floreani et al 2000), Alzheimer's disease and vascular dementia (Polidori et al 2004), and low fruit and vegetable consumption (Al-Delaimy et al 2005).

Carotenoids have also emerged as an excellent tissue marker for a diet rich in fruits and vegetables, and measurement of plasma and tissue carotenoids is considered to have an important role in defining optimal diets (Al-Delaimy et al 2005, Brevik et al 2004, Handelman 2001).

MAIN ACTIONS

Antioxidant

Lutein and zeaxanthin are both powerful antioxidants, with activity having been demonstrated in a number of in vitro and in vivo tests (Higashi-Okai et al 2001, Iannone et al 1998, Naguib 2000, Muriach et al 2008). In vitro studies of human lens epithelial cells also indicate that their antioxidant activity may protect the lens from UVB radiation (Chitchumroonchokchai et al 2004). According to animal studies, lutein increases glutathione levels and reduces retinal apoptosis following ischaemic reperfusion (Dilsiz et al 2005).

Blue light filter

The yellow colour of lutein and zeaxanthin is due to their ability to absorb blue light, which is believed to contribute to their protective function because blue light is at the high energy, and therefore the most damaging, end of the visible spectrum (Krinsky et al 2003). Lutein and zeaxanthin thus serve as 'natural sunglasses' (Rehak et al 2008) that act as an optical filter for blue light, reducing chromatic aberration and preventing damage to the photoreceptor cell layer (Krinsky et al 2003).

Macular pigment development

Lutein and zeaxanthin are entirely of dietary origin and are initially absent in newborns but gradually accumulate over time (Nussbaum et al 1981). It has been generally accepted that macular pigment density decreases with age; however, there are conflicting results. In one prospective, observational study involving 390 patients, macular pigment density was not found to change significantly with age, even when elderly subjects with cataracts and ARMD were considered (Ciulla & Hammond 2004). Other studies, however, have found that macular pigment does indeed decline with age in both normal eyes (Beatty et al 2001, Bernstein et al 2002) and those with ARMD (Bernstein et al 2002) and Stargardt macular dystrophy (Zhao et al 2003), but not in retinitis pigmentosa or choroideremia (Zhao et al 2003).

Although lutein and zeaxanthin levels in the serum, diet and retina correlate, the nature of the relationships between lutein and zeaxanthin in foodstuffs, blood and the macula are confounded by many variables, including processes that influence digestion, absorption and transport and accumulation and stabilisation of the carotenoids in the tissues (Beatty et al 2004). It is suggested, however, that lutein and zeaxanthin are transported into an individual's retina in the same proportions found in his or her blood (Bone et al 1997). Two clinical

studies have demonstrated that increasing lutein intake will increase macular pigment density within 4 weeks (Berendschot et al 2000, Hammond et al 1997). Clinical studies have confirmed the association between macular pigmentation, dietary lutein intake and serum lutein levels (Burke et al 2005, Mares et al 2006). However, in small clinical trials, lutein supplementation did not produce improvement in visual function in people with healthy eyes (Bartlett & Eperjesi 2008, Rosenthal et al 2006) or improvement in contrast sensitivity in people with ARMD (Bartlett & Eperjesi 2007). In another trial, however, lutein supplementation was seen to improve visual performance at low illumination, yet this was not correlated with macular pigment density (Kvansakul et al 2006).

Immunomodulation

Lutein modulates cellular and humoral-mediated immune responses, according to animal studies (Kim et al 2000a, 2000b). In particular, high levels of C-reactive protein and a high white blood cell count have been identified in individuals with low serum levels of lutein (Gruber et al 2004). In a case-controlled study, serum lutein and zeaxanthin, together with other carotenoids, were also found to be lower in children with acute phase infections compared to healthy controls (Cser et al 2004).

Photoprotection

According to animal studies, lutein reduces the risk of sunburn, as well as the local UVB radiation-induced immune suppression and reactive oxygen species generation (Lee et al 2004), as well as directly protecting against photoageing and photocarcinogenesis (Astner et al 2007). A protective effect on skin cancer, however, has not been observed in human cohort studies. One prospective cohort study involving 43,867 men and 85,944 women found no significant inverse association between intake of lutein and squamous cell carcinoma (Fung et al 2003), while an increased risk of squamous cell carcinoma was observed for people with multiple prior non-melanoma skin cancers and high serum levels of lutein and zeaxanthin (Dorgan et al 2004).

While a protective effect against skin cancer is uncertain, there is evidence to suggest that supplementation with lutein and zeaxanthin may improve general skin health and simultaneously help to minimise signs of premature ageing (Maci 2007). A double-blind, placebo-controlled study that examined surface lipids, hydration, photoprotective activity, skin elasticity and skin lipid peroxidation found that oral and/or topical administration of either lutein or zeaxanthin provided antioxidant protection with the greatest protection being seen with combined administration of lutein and zeaxanthin (Palombo et al 2007). The clinical significance of these findings is uncertain.

CLINICAL USE

Age-related macular degeneration

The evidence that lifetime oxidative stress plays an important role in the development of ARMD is now compelling (Hogg & Chakravarthy 2004). ARMD is thought to be the result of free radical damage to photoreceptors within the macula, and therefore it is suspected that inefficient macular antioxidant systems play a role in disease development. Low levels of lutein and zeaxanthin in the diet, serum or retina, as well as excessive exposure to blue light and cigarette smoking, are therefore considered to increase the risk of ARMD (Bone et al 2003); however, an 18-year prospective follow-up study of 71,494 women and 41,564 men aged >50 years found that lutein/zeaxanthin intake as assessed by a semiquantitative food-frequency questionnaire was not associated with the risk of self-reported early ARMD (Cho et al 2008). Interestingly, two case-controlled studies have found that lycopene, rather than lutein or zeaxanthin, was reduced in the serum of ARMD patients (Cardinault et al 2005, Mares-Perlman et al 1995). It was suggested that this result could be due to antioxidant protection of lutein and zeaxanthin by lycopene or different dietary habits.

Epidemiological and autopsy studies have found an inverse relationship between lutein and zeaxanthin intake and macular pigment density (Bone et al 2001, Curran-Celentano et al 2001). The presence of unusually high levels of macular carotenoids in older donors who were regularly consuming high-dose lutein supplements further supports the hypothesis that long-term lutein supplementation can raise levels of macular pigment (Bhosale et al 2007).

Plasma lutein and macular pigment density have been demonstrated to increase with lutein supplementation in ARMD patients (Bernstein et al 2002, Wang et al 2007) and healthy controls (Koh et al 2004), suggesting that a diseased macula can accumulate and stabilise lutein and/or zeaxanthin (Koh et al 2004) and that ARMD is not associated with intestinal malabsorption of carotenoids. This has led to the suggestion that abnormalities in the metabolism of lutein and zeaxanthin in ARMD may reside in the uptake of lutein and zeaxanthin from the plasma and transport into the retina (Wang et al 2007). This is supported by a lutein and zeaxanthin supplementation study that found that macular pigment density did not increase in many subjects despite rises in serum concentrations (Trieschmann et al 2007).

While conclusive evidence as to whether increased intake of lutein or zeaxanthin will reduce the incidence of ARMD is still unavailable (Berendschot et al 2002, Broekmans et al 2002, Hammond et al 1997), recent studies have produced encouraging results for people with preexisting ARMD. Improvements of up to 92% in visual acuity tests were observed when subjects consumed a diet designed to contain approximately 150 g of spinach 4–7 times a week (Richer 1999), and in 30 patients with early ARMD and visual acuity of 6/9 or better daily supplementation with lutein, vitamin E and nicotinamide for 180 days improved macular function (Falsini et al 2003).

The results from the Lutein Antioxidant Supplementation Trial provide further support for lutein supplementation in ARMD (Richer et al 2004). This was a double-blind, randomised, placebo-controlled study involving 90 subjects

Clinical note — Age-related macular degeneration (ARMD)

ARMD is the leading cause of blindness in people over 65 years of age (Pratt 1999). Its exact aetiology is unknown; however, several risk factors have been established such as lighter iris colour, positive family history, lifestyle factors (e.g. cigarette smoking), hypertension, female gender and low serum concentrations of carotenoids (Cardinault et al 2005). The disease causes a loss of central vision and can impair most activities essential for independent living, such as reading, driving and writing. The prevalence of ARMD and its social and economic consequences are increasing in line with the ageing population.

with atrophic ARMD who were given 10 mg lutein, 10 mg lutein plus broad-spectrum antioxidants/vitamins/minerals, or placebo for 1 year. At baseline and every 4 months during the study period, subjects were examined for changes in macular pigment density, photostress recovery, contrast sensitivity and visual acuity. Both the lutein and lutein plus antioxidant groups achieved an increase of 36% and 43%, respectively, in macular pigment density, whereas the placebo group experienced a slight decrease. Significant improvements in visual acuity, objective visual function parameters, photostress recovery and contrast sensitivity were also observed with lutein therapy (Richer et al 2004).

Cataracts

Lens density has been found to inversely correlate to macular lutein and zeaxanthin levels (Hammond et al 1997) and numerous observational studies have found that increased consumption of foods high in lutein and zeaxanthin is associated with a decreased risk for cataracts (Brown et al 1999, Tavani et al 1996, Delcourt et al 2006). In one study involving 77,466 female nurses from the Nurses' Health Study, those with the highest quintile for consumption of zeaxanthin and lutein were found to have a 22% reduction in the risk of cataract extraction (Chasan-Taber et al 1999). Similarly, a study of 1802 women aged 50–79 found that women in the highest quintile category of diet or serum levels of lutein and zeaxanthin were 32% less likely to have nuclear cataract as compared with those in the lowest quintile category (Moeller et al 2008). A further epidemiological study of 3271 Melbourne residents found that while cortical and posterior subcapsular cataracts were not significantly associated with lutein or zeaxanthin intake, high dietary lutein and zeaxanthin intake was inversely associated with the prevalence of nuclear cataract (Vu et al 2006). The link between lutein and cataracts is further supported by a small randomised, placebo-controlled trial of 17 patients with clinically diagnosed age-related cataracts that found that supplementation with lutein 15 mg three times weekly for up to 2 years resulted in improved visual performance (visual acuity and glare sensitivity) compared with placebo (Olmedilla et al 2003).

These results contrast with those from a cohort study of 478 women without previously diagnosed cataracts, which failed to detect a significant inverse relationship between lutein intake and lens opacities over a 13–15-year follow-up period (Jacques et al 2001).

Retinitis pigmentosa

In a double-masked, randomised, placebo-controlled crossover trial, supplementation with 10 mg/day for 12 weeks followed by 30 mg/day for 12 weeks was found to improve visual field and possibly visual acuity in 34 patients with retinitis pigmentosa (Bahrami et al 2006). A further study found that daily supplementation with 40 mg of lutein over 9 weeks followed by 20 mg for a further 16 weeks significantly improved visual acuity in 16 subjects with retinitis pigmentosa, many of whom were also taking other supplements (Dagnelie et al 2000).

Atherosclerosis

Oxidative modification of LDL in the vascular wall seems to be a key factor in atherosclerosis development and thus lipid-soluble antioxidants that can protect LDLs may have a role in atherosclerosis prevention (Cherubini et al 2005); however, the relationship between lutein and zeaxanthin status and atherosclerosis is unclear.

Plasma levels of lutein, beta-cryptoxanthin and zeaxanthin were correlated to carotid intima–media thickness in a 3-year case-controlled study of 231 subjects (Iribarren et al 1997), as well as in an 18-month epidemiological study of 573 subjects, suggesting that these carotenoids may be protective against early atherosclerosis (Dwyer et al 2004). Lutein intake has also been found inversely associated with the risk of ischaemic stroke in an observational study involving 43,738 males (Ascherio et al 1999), as well as being inversely associated with the risk of subarachnoid haemorrhage in a cohort study of 26,593 male smokers (Hirvonen et al 2000). Serum levels of lutein and zeaxanthin, however, were not associated with atherosclerosis risk in a case–control study involving 108 cases of aortic atherosclerosis in an elderly population (Klipstein-Grobusch et al 2000).

The foregoing findings contrast with those from two case-controlled studies that found a positive correlation between lutein and zeaxanthin levels and cardiovascular risk. A nested, case–control study of 499 cases of cardiovascular disease with matched controls taken from the Physicians' Health Study found that concentrations of plasma lutein, zeaxanthin and retinol corresponded to a moderate increase in cardiovascular disease (Sesso et al 2005). Similarly, myocardial infarction risk was positively associated with lutein and zeaxanthin levels in adipose tissue and the diet in a case-controlled study of 1456 cases of first acute myocardial infarction and matched controls (Kabagambe et al 2005). The clinical significance of these findings is unclear and requires further investigation.

Alzheimer's dementia

Dementia has been found to be associated with increased protein oxidative modification and the depletion of a large spectrum of antioxidant micronutrients, including lutein and zeaxanthin (Polidori et al 2004). A clinical study of 25 subjects with mild cognitive impairment, 63 subjects with AD and 56 healthy individuals found that serum lutein levels were lowest in the first two groups, particularly those with AD (Rinaldi et al 2003), while a double-blind trial of 49 women aged 60–80 years found improved cognitive function after supplementation with a combination of docosahexaenoic acid and lutein (Johnson et al 2008).

Cancer prevention

High dietary intake of lutein has been associated with reduced risk of some cancers, most notably endometrial and ovarian cancer, but not all cancers, according to epidemiological evidence (Freudenheim et al 1996, Fung et al 2003, Gann et al 1999, Giovannucci et al 1995, Huang et al 2003, Ito et al 2003, Lu et al 2001, McCann et al 2000, Michaud et al 2000, Nomura et al 1997, Schuurman et al 2002, Terry et al 2002).

Lung cancer

The link between carotenoid intake and lung cancer has undergone extensive scrutiny and extensive epidemiological evidence suggests a reduction in lung cancer risk with high dietary intake of carotenoids (Cooper et al 1999). Initial research used food composition tables and therefore focused on beta-carotene, for which data were available; however, the dietary intake of beta-carotene and other carotenoids such as lutein and zeaxanthin is highly correlated (Ascherio et al 1992) and as food composition data for these nutrients have become available, studies have suggested a link between dietary lutein intake and reduced lung cancer risk (Cooper et al 1999).

Three large population studies of diet and lung cancer have revealed a non-significant association between high lutein intake and lower risk of lung cancer (Ito et al 2003, Michaud et al 2000, Ziegler et al 1996), and a significant trend was observed in another population-based case–control study (Le Marchand et al 1993). A nested case–control study also found that serum lutein and zeaxanthin were lower in those with lung cancer than in controls (Comstock et al 1997). These results are contrasted with those from a case–control study of 108 cases of lung cancer in a Chinese occupational cohort that found that higher serum carotenoid levels, including lutein and zeaxanthin, were significantly associated with increased lung cancer risk among alcohol drinkers, while having a possible protective association among non-drinkers (Ratnasinghe et al 2000).

Cervical cancer

A recent systematic review suggests that lutein/zeaxanthin is likely to have a protective effect for cervical neoplasia and possibly for human papilloma virus persistence (Garcia-Closas et al 2005).

Endometrial cancer

An epidemiological study involving 232 patients with endometrial cancer and 639 controls found that an intake of more than 7.3 mg/day of lutein was associated with a 70% reduced risk of endometrial cancer (McCann et al 2000).

Ovarian cancer

A case–control study found that weekly intake of lutein of more than 24 mg was associated with a 40% reduction in the risk for developing ovarian cancer compared with weekly consumption of less than 3.8 microgram (Bertone et al 2001).

Breast cancer

High lutein and zeaxanthin intake has been related to reduced risk of breast cancer (Dorgan et al 1998, Toniolo et al 2001). High lutein intake (> 7 mg/day) was associated with a 53% reduction in the risk of developing breast cancer compared with low consumption (< 3.7 mg/day) in a population-based case–control study of 608 premenopausal women over age 40 (Freudenheim et al 1996). Similar risk reductions were found in a nested case–control study of 540 New York women (Toniolo et al 2001) and another nested case–control study of 969 cases of breast cancer and matched controls from the Nurses' Health Study found that the risk of breast cancer was 25–35% less for women with the highest quintile compared with that for women with the lowest quintile of lutein/zeaxanthin and total carotenoid intake (Tamimi et al 2005). Although this association is encouraging, another study of 4697 women followed over 25 years found no significant relationships between lutein intake and breast cancer risk (Jarvinen et al 1997).

Gastric cancer

High serum lutein levels have been associated with a higher incidence of gastric carcinoma, according to a cohort study of 29,584 patients with oesophageal and stomach cancer (Abnet et al 2003); however, this association requires further investigation.

Bowel cancer

The relationship between lutein and zeaxanthin intake and colon cancer is uncertain. A case–control study involving 1993 cases of colon cancer and 2410 controls found that lutein intake, as measured by a food-frequency score, was inversely associated with colon cancer and another case–control study of 223 subjects with histologically confirmed colon or rectal cancer identified a non-significant inverse association with lutein (Levi et al 2000). A cohort analysis of 5629 women, however, found no such association (Terry et al 2002). More recently, a case-controlled study found that women with high intakes of long-chain polyunsaturated fatty acids had an inverse association between lutein and zeaxanthin intake and the risk of colon cancer (Nkondjock & Ghadirian 2004). Further investigation is required to clarify these findings because animal studies suggest low doses of lutein inhibit aberrant crypt foci formation, whereas high doses may increase the risk by 9–59% (Raju et al 2005).

Prostate cancer
Overall, epidemiological evidence suggests that lutein and zeaxanthin intake has no influence over the risk of prostate cancer (Bosetti et al 2004, Gann et al 1999, Giovannucci et al 1995, Huang et al 2003, Lu et al 2001, Nomura et al 1997, Schuurman et al 2002). However, when lutein was included as part of a mixed carotenoid and tocopherol extract, the combination was effective in an in vitro study of prostate cancer cell lines (Lu et al 2005) and a case-controlled study of 130 patients with adenocarcinoma of the prostate found that prostate cancer risk was seen to decline with increasing consumption of carotenoids, including lycopene, alpha-carotene, beta-carotene, beta-cryptoxanthin, lutein and zeaxanthin (Jian et al 2005).

Laryngeal cancer
A case–control study involving 537 subjects identified an inverse relationship between dietary lutein and zeaxanthin intake, together with the intake of other carotenoids, and the risk of laryngeal cancer (Bidoli et al 2003).

OTHER USES
Lutein and zeaxanthin may be used as part of a general antioxidant supplement, often taken in conjunction with other carotenoids in cases where there is known or suspected increased oxidative load.

DOSAGE RANGE

According to clinical studies
- Macular protection: lutein 6–20 mg/day; zeaxanthin 2–5 mg/day.
- Cataracts — improving visual performance: lutein 15 mg three times weekly.

TOXICITY
There is strong evidence for the safety of lutein at intakes up to 20 mg/day, although much higher levels have been tested without adverse effects and may be safe (Shao & Hathcock 2006).

ADVERSE REACTIONS
Insufficient reliable information available.

SIGNIFICANT INTERACTIONS

Vitamin C
Lutein showed increased antioxidant efficacy with vitamin C in an animal study (Blakely et al 2003). Further to this, a small in vivo study showed 2000 mg of vitamin C enhanced the absorption of lutein (Tanumihardjo et al 2005).

Vitamin E
Vitamin E showed increased antioxidant efficacy with lutein according to an animal study (Blakely et al 2003).

Phytosterols
High dietary intake of phytosterol esters (6.6 g/day) reduced plasma levels of lutein by 14% in a small clinical trial; however, this was reversed by increasing fruit and vegetable intake (Clifton et al 2004).

Orlistat
Theoretically, long-term use of orlistat leads to reduced plasma levels of lutein due to reduced gastric absorption (Australian Medicines Handbook) — increased dietary intake of lutein should be considered.

Olestra
Lutein and zeaxanthin levels have been found to decrease with long-term use of olestra (Tulley et al 2005) — increased dietary intake of lutein should be considered.

CONTRAINDICATIONS AND PRECAUTIONS
Lutein and zeaxanthin are contraindicated in people with a hypersensitivity to these carotenoids or their food sources.

PREGNANCY USE
Eating dietary amounts of foods rich in lutein and zeaxanthin is likely to be safe. Women at risk of premature rupture of the membranes are cautioned against very high intake because one study observed a fourfold greater risk of membrane rupture with high serum lutein levels (Mathews & Neil 2005).

PATIENTS' FAQs
What will this supplement do for me?
Lutein and zeaxanthin are important for eye health and may also reduce the risk of developing endometrial and ovarian cancer over time.
When will it start to work?
Increased intake of lutein can improve macular health within 4 weeks; however, clinical effects

PRACTICE POINTS/PATIENT COUNSELLING
- Lutein and zeaxanthin are antioxidant carotenoids found in spinach, corn, egg yolk, squash and greens.
- Lutein and zeaxanthin are essential for the development of macular pigment, which protects photoreceptor cells in the retina from free radical damage.
- Epidemiological studies have generally found an inverse relationship between lutein and zeaxanthin intake and macular degeneration; however, conclusive evidence as to whether increased intakes will reduce the incidence of ARMD is still unavailable.
- One controlled study has found that long-term use of lutein supplements may increase visual performance in people with preexisting cataracts.
- High dietary intake of lutein has been associated with reduced risk of some cancers, most notably endometrial and ovarian cancer, but not all cancers, according to epidemiological evidence.
- Supplements containing lutein and zeaxanthin should be taken with food as dietary fat improves their absorption.

develop slowly and may not be detected for 6 months. In regard to improving visual performance in people with preexisting cataracts, effects take even longer (≈2 years).

Are there any safety issues?

Lutein and zeaxanthin are generally considered safe.

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Lycopene

BACKGROUND AND RELEVANT PHARMACOKINETICS

Lycopene is a fat-soluble, non-provitamin A carotenoid that imparts the red colour to tomato, guava, rosehip, watermelon and pink grapefruit. Animals and humans do not synthesise lycopene, so they must depend on dietary sources. Research shows that bioavailability of lycopene varies depending on factors such as food source, other foods in the diet, the presence of other carotenoids and dietary fat, cooking temperatures and processing.

Processing, and heating in particular, has been found to significantly increase lycopene bioavailability, as it induces the isomerisation of lycopene from

the *trans*- to *cis*-configuration (Shi & Le Maguer 2000). In other words, lycopene is best absorbed from tomato products such as pastes and sauces, rather than from unprocessed fresh tomatoes.

Lycopene is widely distributed in the human body and is one of the major carotenoids found in human serum (between 21% and 43% of total carotenoids). High concentrations are found in the adrenal gland and testes, although significant amounts are also found in the liver, adipose tissue, prostate, kidney and ovaries (El Sohemy et al 2002, Gerster 1997, Johnson 1998, Stahl et al 1992). Lycopene has also been detected in high concentrations in ciliary body and retinal pigment epithelium (Khachik et al 2002).

CHEMICAL COMPONENTS

Lycopene is a 40-carbon acyclic carotene with 11 conjugated and 2 unconjugated double bonds, normally in the all-*trans*-configuration, but the double bonds are subject to isomerisation, and various *cis*-isomers (mainly 5, 9, 13 or 15) are found in plasma and plants (Holloway et al 2000). The *cis*-isomer has better bioavailability from foods.

FOOD SOURCES

The richest sources of lycopene are red tomatoes and processed tomato products. Other sources include watermelon, pink grapefruit and papaya. The lycopene content of food depends on the cultivars grown and the growing conditions.

It is currently estimated that daily intake from all dietary sources ranges between 0.5 and 27 mg/person/day or 0.08 and 0.45 mg/kg/day (Jonker et al 2003).

DEFICIENCY SIGNS AND SYMPTOMS

Although lycopene is not considered an essential nutrient, it is important for wellbeing and optimal health. As such, deficiency signs and symptoms are unknown.

MAIN ACTIONS

Antioxidant

The many conjugated double bonds of lycopene make it a powerful antioxidant (particularly against singlet oxygen and free radicals) and its activity in vitro is nearly twice as great as beta-carotene (Cantrell et al 2003, Shi & Le Maguer 2000, Tsen et al 2006).

Reduces LDL cholesterol levels and lipid oxidation

A significant 14% reduction in plasma LDL cholesterol concentrations has been shown for a dose of 60 mg/day lycopene taken over 3 months by healthy volunteers. While the mechanism of action is unclear, in vitro testing suggests 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibition and enhancement of LDL receptor activity in macrophages (Fuhrman et al 1997). Lycopene also prevents oxidation of lipids and LDL cholesterol, according to a clinical study by Agarwal & Rao (1998). Lycopene may also reduce the formation of macrophage foam cells induced by modified LDL, via decreasing lipid synthesis and downregulating the activity and expression of scavenger receptor A, according to in vitro tests (Napolitano et al 2007).

Chemopreventative activity

Anticancer activity of lycopene has been demonstrated in cell and tissue culture studies and animal tumour models. These studies indicate that lycopene has multiple mechanisms of action, some of which remain to be fully elucidated. Lycopene appears to inhibit human cancer cell growth by interfering with growth factor receptor signalling and cell cycle progression (Fornelli et al 2007, Heber & Lu 2002, Stahl et al 2000). In vitro and in vivo evidence supports the theory that antiproliferative activity is achieved by upregulation of a gene, connexin 43, which restores direct intercellular gap junctional communication, usually deficient in many human tumours. This restoration of normal intercellular gap junctional communication is associated with decreased proliferation. Lycopene is also thought to inhibit proliferation of cancerous cells by arresting cell cycle progression, particularly at the G_1 phase, which is often up-regulated in cancer cells (Ivanov et al 2007, Nahum et al 2006, Park et al 2005). One possible mechanism for this is via the attenuation of cyclin Dl levels which acts as a growth factor sensor in G_1 phase and subsequently inhibit the action on insulin-like growth factor-1 (IGF-1)-induced cell cycle progression (Nahum et al 2006). Increased levels of IGF-1 production have been associated with an increased risk of cancer. Lycopene has been shown to decrease levels of IGF-1 (Liu et al 2008, Walfisch et al 2007), by affecting the IGF-binding proteins (IGFBPs) (Kanagaraj et al 2007, Vrieling et al 2007). However, other studies have reported that the IGFBPs made no difference to IGF-1 levels (Graydon et al 2007, Voskuil et al 2008). Investigation using animal models also suggests that lycopene may exert its chemopreventative effects by modulating lipid peroxidation and enhancing the activities of phase 2 enzymes, specifically those in the glutathione redox cycle (Bhuvaneswari et al 2001, Bhuvaneswari & Nagini 2005, Lian & Wang 2008, Velmurugan et al 2002). A cell culture study using endometrial, mammary and lung human cancer cells has identified that lycopene has stronger antiproliferative activity than alpha- and beta-carotenes (Levy et al 1995). Several in vitro studies have indicated that lycopene may have chemotherapeutic activity by promoting cancer cell apoptosis (Hantz et al 2005, Ivanov et al 2007, Kanagaraj et al 2007, Salman et al 2007). Another possible protective mechanism of lycopene is to promote methylation modulation of gene expression in several breast cancer cell lines (King-Batoon et al 2008). Lycopene may also have an anti-metastatic action in high doses (Hwang & Lee 2006, Huang et al 2007, 2008), but not at physiological doses (Burgess et al 2008).

Of special significance in prostate cancer prevention is the finding that lycopene interferes with local testosterone activation by reducing the expression of 5-alpha-reductase I in prostate tumours in a rat model (Siler et al 2004). As a consequence,

several androgen target genes in the tumours were drastically downregulated.

OTHER ACTIONS

The Antioxidant Supplementation in the Atherosclerosis Prevention (ASAP) study showed that low plasma levels of lycopene were associated with an 18% increase in intima–media thickness (IMT) of the common carotid artery wall in men as compared with men in whom plasma levels were higher than median (Rissanen et al 2002). Lycopene also shows anti-inflammatory activity (Bhuvaneswari & Nagini 2005) and antifungal action in vitro (Sung et al 2007).

A reduction in cyclosporine-induced nephrotoxicity and testicular toxicity has been identified in experimental models for lycopene (Atessahin et al 2007, Türk et al 2007). Lycopene also demonstrates protection against gentamycin-induced nephrotoxicity (Karahan et al 2005).

CLINICAL USE

The clinical effects of lycopene are studied in relation to dietary intake and oral supplementation. It should be noted that the assessment of dietary lycopene intake varies with the method used to collect dietary information and the food composition databases used to estimate nutritional content (Shils 2006).

Cancer prevention

Lycopene is often included as an ingredient in antioxidant combination supplements and is thought to contribute to risk reduction for cancer. Some studies have investigated the effects of lycopene on risk of disease, although many consider it as part of the carotenoid group and study its effects in this way. Increasingly, interventional studies with supplemental lycopene are being conducted in an attempt to determine whether stronger protective or treatment effects will ensue. Several cancers, in particular, are being targeted in research: these are prostate, stomach, cervix and breast cancers.

Total cancer risk

A 2002 Japanese study involving 2444 people who were followed for 9 years found that high serum levels of lycopene, total carotenes and carotenoids were significantly and inversely associated with subsequent mortality from all causes and cancers of all sites after adjusting for gender, age and serum levels of total cholesterol, alpha-tocopherol and retinol (Ito et al 2002).

Prostate cancer

Prospective and retrospective epidemiological studies generally indicate an inverse relationship between lycopene intake and prostate cancer risk, which is also supported by in vitro and in vivo experiments showing that oral lycopene is bioavailable, accumulates in prostate tissue, is localised to the nucleus of prostate epithelial cells and demonstrates multiple mechanisms of chemoprevention (Chan et al 2009, van Breemen & Pajkovic 2008).

A meta-analysis of 11 case–control studies and 10 cohort studies or nested case–control studies suggested there is a modest protection from prostate cancer with increased consumption of lycopene from tomato and tomato-based products, although results are not yet definitive. The association is stronger for cooked tomato products compared to raw, and in those with higher levels of serum lycopene (Etminan et al 2004).

More specifically, five studies found a 30–40% reduction in prostate cancer risk associated with high tomato or lycopene consumption, three found a non-significant 30% reduction in risk and seven were not supportive of an association. The largest epidemiological study was conducted by the Harvard Medical School, which assessed the diets of 47,894 volunteers and identified several foods as significantly associated with lower prostate cancer risk (Giovannucci et al 1995). They were tomato sauce, tomatoes and pizza, which are primary sources of lycopene. Additionally, consumption of more than 10 servings per week was required for protective effects to be observed.

A nested-controlled study within the European Prospective Investigation into Cancer and Nutrition (EPIC) study involving 966 cases and 1064 controls found an inverse association between plasma lycopene and the risk of advanced prostate cancer (Key et al 2007). According to one study, the protective effect of lycopene-containing foods may be synergistically enhanced by the consumption of green tea (Jian et al 2007). Risk reduction was also observed for men with a family history of prostate cancer having increased consumption of lycopene in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial ($n = 29,361$) (Kirsh et al 2006). However, no association was found between prostate cancer risk and dietary intake of either lycopene or total tomato-based products for the general study population.

Intervention studies

Besides the epidemiological data on primary prevention, there are some reports of short- to medium-term clinical intervention trials with lycopene supplement or tomatoes, although results are mixed. A small study of men with high-grade prostate intraepithelial neoplasia (HGPIN), a precursor of prostate cancer, showed that supplementation with 4 mg lycopene twice daily for 1 year had a chemopreventative effect, preventing progression of HGPIN to prostate cancer (Mohanty et al 2005). Three of four studies found that either lycopene or tomatoes significantly reduces serum levels of prostate-specific antigen (PSA) (Ansari & Gupta 2004, Bowen et al 2002, Clark et al 2006, Kucuk et al 2002). Kucuk et al conducted a randomised study involving 26 men, which found that taking a tomato oleoresin extract containing 30 mg lycopene for 3 weeks resulted in smaller prostate tumours, less involvement of surgical margins and/or extra-prostatic tissues with the cancer and less diffuse involvement of the prostate by high-grade prostatic intraepithelial neoplasia compared with controls (Kucuk et al 2001). Additionally, plasma PSA levels were reduced. Another study, by Bowen et al (2002), involving 32 patients with

localised prostate cancer found that consuming tomato sauce-based pasta dishes for 3 weeks (providing 30 mg lycopene/day) reduced serum PSA levels by 17.5% and, overall, significantly reduced DNA damage in both leucocyte and prostate tissue. A lycopene supplement (Lycored softules) for 3 months in 20 patients with metastatic hormone refractive prostate cancer (HRPC) significantly reduced PSA levels and provided relief in bone pain and lower urinary tract symptoms (Ansari & Gupta 2004). HRPC was defined as an increase in PSA levels of more than twice the normal value (0–4 ng/mL) confirmed in two consecutive determinations at 2-week intervals in the presence of castrate levels of testosterone. Interestingly, a study involving men with prostate cancer and increasing PSA levels (in three consecutive readings) showed that treatment with lycopene (15 mg/day) leads to stabilisation in PSA levels after 6 months of treatment, but no reductions after this point (Vaishampayan et al 2007).

In contrast, several studies have found no change in PSA levels with lycopene interventions. One was a dose-escalating study of 36 men, which tested high doses of lycopene in biochemically relapsed prostate cancer (Clark et al 2006). The doses studied were 15, 30, 45, 60, 90 and 120 mg/day taken for 1 year and significant elevations of plasma lycopene were noted at 3 months and then appeared to plateau for all six dose levels. Similarly, no change in PSA was found in men with high-grade prostatic intraepithelial neoplasia, atypical foci or repeated non-cancerous biopsies, after 4 months' treatment with 30 mg/day lycopene (Lyc-O-Mato®) plus a multivitamin compared to those given the multivitamin alone. Interestingly, PSA levels decreased after the first month of treatment with lycopene, but returned to baseline levels after 4 months (Bunker et al 2007). A lycopene-rich tomato supplement (30 mg lycopene/day) failed to reduce PSA levels in men with androgen-independent prostate cancer given after 4 months (Jatoi et al 2007).

Stomach

Mixed results have also been seen in studies investigating whether lycopene reduces the incidence of stomach cancer (De Stefani et al 2000, Garcia-Closas et al 1999, Jenab et al 2006, Persson et al 2008, Tsugane et al 1992, Yuan et al 2004).

The relationship between pre-diagnostic serum levels of carotenoids and risk of gastric cancer was determined in a study involving 761 middle-aged or older men in Shanghai, China, with a follow-up of 12 years (Yuan et al 2004). High serum levels of alpha- and beta-carotenes and lycopene were significantly associated with reduced risk of developing gastric cancer (all P values for trend ≤ 0.05), whereas no statistically significant relationships among the serum levels of beta-cryptoxanthin, lutein/zeaxanthin, retinol, alpha-tocopherol and gamma-tocopherol were identified with gastric cancer risk. A recent large nested-control study produced a different result and found no inverse relationship between serum lycopene and gastric cancer risk (Jenab et al 2006). Similarly, no association was found between plasma lycopene levels and gastric cancer risk in a large nested case–control study of 36,745 Japanese subjects (aged 40–69) with *Helicobacter pylori* infection (Persson et al 2008). It is possible that protective effects of lycopene are only seen in populations with low baseline levels such as China.

Cervix

Results from two case–control studies have found an association between low serum lycopene levels and existing cervical cancer, but it is uncertain whether this can be interpreted as a risk factor because depleted levels may be a result of tumour usage, the increased burden of oxidative stress or both (Nagata et al 1999, Palan et al 1996).

Breast

Dorjgochoo et al (2008) prospectively investigated the association of plasma levels of tocopherols, retinol and carotenoids with the risk of developing breast cancer among Chinese women (Dorjgochoo et al 2008). The study evaluated 365 incident breast cancer cases and 726 individually matched controls nested within a large cohort study of women aged 40–70 years at baseline. An inverse association was identified between high levels of plasma lycopene (other than *trans*, 5- and 7-*cis* or *trans*-alpha-cryptoxanthin) and risk of developing breast cancer.

Protection against chemotherapy-induced toxicity

Chemotherapy-induced toxicity resulting in organ damage can limit a patient's ability to tolerate full-dose treatment and have long-lasting effects. Efforts to reduce toxicity to enable patients to receive full treatment cycles and preserve quality of life after cancer are actively being sought. Studies with animals suggest that lycopene may be one such protective agent. Lycopene has demonstrated protection against a variety of chemotherapy-induced toxicities such as: cardiotoxicity induced by doxorubicin (Anjos Ferreira et al 2007) and adriamycin (Yilmaz et al 2006); spermiotoxicity induced by cisplatin (Atessahin et al 2006a) and adriamycin (Atessahin et al 2006b); and renal toxicity induced by adriamycin (Yilmaz et al 2006). Further studies are required to confirm that lycopene will not diminish treatment efficacy.

Prevention of cardiovascular disease

Epidemiological studies have generally shown an inverse relationship between tissue and serum levels of lycopene and risk of acute coronary event or stroke and degree of IMT of the common carotid artery (Kohlmeier et al 1997, Rissanen et al 2002, 2003, Sesso et al 2004, 2005).

Strong population-based evidence comes from the large Women's Health Study (n = 39,876), the European Community Multicenter Study on Antioxidants, Myocardial Infarction and Breast Cancer (EURAMIC) study and the Kuopio Ischaemic Heart Disease Risk Factor study (Kohlmeier et al 1997, Rissanen et al 2003, Sesso et al 2004).

In the Women's Health Study, higher plasma lycopene concentrations were associated with a lower risk of cardiovascular disease (Sesso et al 2004). Specifically, for cardiovascular disease, exclusive of angina, women in the upper three quartiles had a significant multivariate risk reduction of 50% compared with those in the lowest quartile. For the EURAMIC study, 1379 individuals (662 patients, 717 controls) from 10 European countries were recruited (Kohlmeier et al 1997). Needle aspiration biopsy samples of adipose tissue were taken shortly after myocardial infarction, and levels of alpha- and beta-carotenes, lycopene and alpha-tocopherol were measured. After adjusting for age, body mass index, socioeconomic status, smoking, hypertension, and maternal and paternal histories of heart disease, only lycopene levels were found to be protective. The effect also appeared to be dose dependent. In contrast, Sesso et al (2005) found no association between plasma lycopene concentrations and cardiovascular disease in middle-aged and older men in a prospective, nested, case–control study (Sesso et al 2005).

In the Kuopio Ischaemic Heart Disease Risk Factor study, 1028 middle-aged men (aged 46–64 years) from Finland were examined and classified into quartiles according to their serum lycopene concentration (Rissanen et al 2003). The men in the lowest quartile had a significantly higher mean IMT of the common carotid artery (CCA-IMT) and maximal CCA-IMT than the others. Once again, a dose-dependent effect was observed as the mean and maximal CCA-IMT increased linearly across the quarters of serum lycopene concentration. This particular finding is important because increased IMT of the CCA has been shown to predict coronary events.

Reducing risk of macular degeneration

Lycopene supplements are sometimes used to reduce the risk of developing macular degeneration and generally support eye health. In general, it is taken in combination with other carotenoids, such as zeaxanthin and lutein, for this indication, for which there is supportive evidence (Cardinault et al 2005). Few studies are available to determine whether lycopene as a sole agent exerts clinically significant protective effects. One cohort study of 159 older people found no inverse association between lycopene intake and 5-year incidence of early age-related macular degeneration (ARMD) (Flood et al 2002). Alternatively, a recent study comparing 34 patients with ARMD to 21 control subjects found that of the serum carotenoid concentrations measured, only lycopene was decreased significantly in the serum LDL and HDL fractions ($P < 0.05$).

Cataract prevention

Studies have identified protective effects for lycopene against oxidative changes in human lens epithelial cells in vitro and reduced incidence and grading of cataract in test animals (Gupta et al 2003, Mohanty et al 2002, Pollack et al 1996). A cross-sectional survey of 372 older volunteers also produced positive results, finding that the risk of cortical cataract was lowest in people with the highest plasma concentrations of lycopene (Gale et al 2001). Similarly, Dherani et al (2008) identified that serum lycopene was inversely associated with the risk of developing cataracts in a cross-sectional study of people aged ≥50 years conducted in North India (Dherani et al 2008).

Protection against UV-induced photodamage

Oral ingestion

Long-term supplementation with lycopene or tomato-derived products rich in lycopene for 10–12 weeks is effective in decreasing skin sensitivity to UV-induced erythema in healthy volunteers and may contribute to life-long protection against harmful UV radiation (Stahl et al 2006). This supports the results of earlier studies. Stahl & Sies (2002) demonstrated that increasing lycopene intake to 16 mg/day (using tomato paste) for 10 weeks provided significant protection against erythema formation following UV irradiation, compared with placebo (Stahl & Sies 2002). The protective effects appear to develop slowly, as tests conducted at 4 weeks found no significant changes. Protective effects were also seen in another study that compared the synthetic lycopene with concentrated tomato extract (Lyc-O-Mato) (Aust et al 2005). The daily dose of lycopene was approximately 10 mg/day, which was lower than in the previous study. Again, 12 weeks were required to detect significant protective effects against UV-induced erythema and the effect was more pronounced in the group using a natural lycopene source.

Topical use

Results from an experimental model show that topical lycopene also has protective effects against acute UV-induced photodamage (Andreassi et al 2004, Fazekas et al 2003). Furthermore, it may act as a preventative agent via inhibition of epidermal ornithine decarboxylase activity, reducing inflammatory responses, maintaining normal cell proliferation and possibly preventing DNA damage, as indicated by blocking the necessitating step of apoptosis following UVB injury.

Male infertility

Lycopene is present in seminal plasma and plays a role in protecting the spermatozoa from oxidative stress. Significantly lower levels of lycopene have been found in the seminal fluid of immunoinfertile compared to fertile men (Palan & Naz 1996). In a clinical trial of 30 men aged 23–45 years with idiopathic infertility, supplementation with 2000 microgram lycopene twice daily improved several sperm parameters. After 3 months, 66.6% of cases showed improvement in sperm concentration (median 22 million/mL), 53% in sperm motility (median of 25%) and 46% in morphology (10%), whilst 40% of cases had improvement in all three parameters (Gupta & Kumar 2002).

Gingivitis
Chandra et al (2007) evaluated the effectiveness of lycopene on its own or combined with oral scaling (OS) and placebo with and without OS in the treatment of gingivitis in a randomised double-blind placebo-controlled trial. After 2 weeks, the group receiving lycopene with OS had a significant reduction in the Bleeding Index compared to the placebo group without OS, and both lycopene groups (with and without OS) had significant reductions in the Gingival Index compared to the placebo groups (with and without OS) (Chandra et al 2007).

Asthma
The association between lycopene and asthma is unclear. Some studies have identified lower levels of lycopene in the serum (Riccioni et al 2006, 2007) and whole blood (Wood et al 2005) to be associated with bronchial asthma, whereas other studies have found no association (Ford et al 2004, Schock et al 2003). It is also unclear whether lowered lycopene levels found in some asthmatic individuals are a consequence of the disease or a contributing factor.

The role of lycopene in exercise-induced asthma is controversial. In a randomised placebo-controlled trial, a daily dose of lycopene (30 mg/day for 1 week) in young athletes did not affect lung function after exercise and did not provide any protective effect against difficulty in breathing (measured by forced expiratory volume) compared to the placebo group (Falk et al 2005). However, this finding is in contrast to an earlier double-blind randomised controlled clinical trial, which found that lycopene (Lyc-O-Mato 30 mg/day) for 1 week protected asthmatic subjects against exercise-induced asthma (Neuman et al 2000).

Skin integrity
Low levels of antioxidants appear to be associated with increased roughness of the skin (reflecting increased depth and density of the furrows and wrinkles of the skin). A study involving 20 healthy volunteers aged between 40 and 50 years found higher levels of lycopene in the skin were significantly correlated to better skin integrity (Darvin et al 2008).

Bacterial prostatitis
In an animal model of chronic bacterial prostatitis, concurrent treatment of lycopene and ciprofloxacin (antibiotic) showed a statistically significant decrease in bacterial growth and improvement in prostatic inflammation compared with the control group and the ciprofloxacin-only group (Han et al 2008). The clinical significance of this finding remains to be tested.

Osteoporosis risk
Oxidative stress has been associated with increased risk of osteoporosis. The role of lycopene in reducing bone turnover was examined in a cross-sectional study of 33 postmenopausal women aged 50–60. In a dose-dependant manner, higher serum lycopene levels were associated with lower levels of cross-linked *N*-telopeptides of type I collagen (a marker of bone resorption) and lower protein oxidation. This suggests that lycopene may be beneficial in reducing the risk of osteoporosis in postmenopausal women; however, clinical studies are required to confirm significance (Rao et al 2007).

Benign prostate hyperplasia
A pilot study found that lycopene may inhibit the progression of benign prostatic hyperplasia (BHP). After 6 months of treatment with lycopene (15 mg/day), volunteers had reduced serum PSA levels, improved symptoms and less increase in prostate size (assessed by trans-rectal ultrasonography and digital rectal examination) compared to the placebo group (Schwarz et al 2008).

OTHER USES
General antioxidant nutrient.

DOSAGE RANGE

Based on available evidence
- Hypercholesterolaemia: 60 mg/day.
- One large study on lycopene and prostate cancer suggested that a daily intake of approximately 6.5 mg was protective (Giovannucci et al 1995).
- Sunburn protection: 10–16 mg/day.

TOXICITY
Animal studies have shown that 600 mg lycopene/kg/day is not toxic (Jonker et al 2003). There is good evidence of safety at intakes up to 75 mg/day (the new Observed Safe Level), although much higher levels have been tested without adverse effects (Shao & Hathcock 2006).

ADVERSE REACTIONS
Animal studies have demonstrated that 600 mg lycopene/kg/day does not produce adverse effects and is well tolerated (Jonker et al 2003). This level is far in excess of usual dietary intake in humans.

SIGNIFICANT INTERACTIONS

Drugs reducing fat absorption (e.g. cholestyramine, orlistat)
Drugs that reduce fat absorption, such as cholestyramine, colestipol and orlistat, may also reduce the absorption of lycopene — separate doses by at least 2 h.

CONTRAINDICATIONS AND PRECAUTIONS
Hypersensitivity to lycopene or its food sources.

PREGNANCY USE
Eating dietary amounts of foods rich in lycopene is likely to be safe.

PATIENTS' FAQs
What will this supplement do for me?
Lycopene is an antioxidant vitamin that may reduce the risk of developing some forms of cancer, cardiovascular disease and cataracts. It also protects the skin from sunburn and may reduce cholesterol levels when ingested in high doses.

PRACTICE POINTS/PATIENT COUNSELLING

- Lycopene is a fat-soluble, non-provitamin A carotenoid that imparts the red colour to tomatoes and is most bioavailable from processed food sources such as tomato paste.
- Lycopene has antioxidant and cholesterol-lowering activity and may reduce the risk of developing cardiovascular disease, according to epidemiological evidence.
- Epidemiological evidence generally suggests that higher intakes of tomato-based products reduce the risk of prostate cancer and possibly stomach cancer and cataracts.
- Preliminary evidence suggests that intervention with tomato-enriched products or lycopene may decrease tumour size in localised prostate cancer and reduce PSA levels.
- Increased intake of lycopene has also been associated with reduced risk of cortical cataract and sunburn. Preliminary evidence also suggests topical application of lycopene protects against UV-induced erythema (sunburn).

When will it start to work?

Risk reduction is likely to be a result of many years of consistently high intakes. Protective effects against sunburn have been reported after 10 weeks.

Are there any safety issues?

Safety studies conducted in animals suggest that lycopene is very safe and well tolerated.

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L-Lysine

BACKGROUND

L-Lysine is absorbed from the small intestine and is transported to the liver via the portal circulation where it is involved in protein biosynthesis and is partly metabolised.

CHEMICAL COMPONENTS

L-Lysine is the biologically active stereoisomer of lysine.

MAIN ACTIONS

Essential amino acid

The human body cannot synthesise L-lysine so it must be taken through the diet. The richest sources of L-lysine are animal proteins such as meat and poultry. It is also found to lesser extents in eggs, beans and dairy products (Bratman & Kroll 2000).

Antiviral

L-Lysine has an inhibitory effect on the multiplication of HSV in cell cultures (Griffith et al 1981, Milman et al 1980). It appears to act as an antimetabolite and competes with arginine for inclusion into viral replicative processes (Griffith et al 1981). As such, lysine retards the viral growth promoting action of arginine.

Calcium regulation

L-Lysine may be involved in the cellular absorption, regulation and use of calcium (Civitelli et al 1992). In vitro tests with human osteoblasts indicate that lysine has a positive effect on osteoblast proliferation, activation and differentiation (Torricelli et al 2003).

OTHER ACTIONS

L-Lysine is required for biosynthesis of collagen, elastin and carnitine.

CLINICAL USE

Herpes simplex — prevention and treatment

A number of clinical studies have investigated the effects of oral L-lysine supplementation as prophylaxis or treatment of herpes virus infections, overall producing contradictory results (Digiovanna & Blank 1984, Griffith et al 1978, 1987, McCune et al 1984, Milman et al 1978, 1980, Thein & Hurt 1984, Walsh et al 1983, Wright 1994).

One randomised, double-blind crossover study found that supplementation with 1248 mg/day of L-lysine decreased the recurrence rate of HSV attacks in non-immunocompromised subjects, but did not shorten healing time during an outbreak (McCune et al 1984). Another double-blind trial compared the effects of 1000 mg L-lysine three times daily for 6 months with placebo treatment in 52 subjects. This time, not only was L-lysine found to decrease recurrence rates, but also symptoms were significantly diminished in severity and healing time significantly reduced (Griffith et al 1987). An open study of 45 patients with recurring HSV infection found that L-lysine supplementation accelerated recovery and reduced recurrence. The doses used were between 312 and 1200 mg/day in single or multiple doses (Griffith et al 1978). Thein and Hurt (1984) conducted a 12-month, double-blind crossover trial involving 26 subjects with recurring herpes lesions and found that a dose of 1000 mg/day had protective effects against lesion formation. Furthermore, once supplementation ceased, an increase in lesion frequency occurred. This study went further than others, identifying that serum lysine levels need to exceed 165 nmol/mL in order for clinical effects to become significant.

Two further double-blind studies produced negative results. Doses of 1000 mg or 1200 mg/day

were tested, both failing to produce prophylactic or treatment effects for herpes simplex (Digiovanna & Blank 1984, Milman et al 1980).

However, an epidemiological survey of 1543 volunteers asking about the perceived effectiveness of lysine supplements to treat herpes infections over a 6-month trial period indicated positive results (Walsh et al 1983). Of those people with cold sores or fever blisters, 92% claimed lysine supplements were 'very effective' or 'an effective form' of treatment and 81% of those with genital herpes and who had tried other forms of treatment also claimed positive results.

The effect of lysine on herpes may depend on variables such as the overall dietary ratio of lysine to arginine and the additional dose of supplemental lysine. In practice, doses of > 3000 mg/day are used as treatment during an acute episode, based on the positive findings of the Griffith study. This is combined with a diet low in arginine-rich foods, such as chocolate, peas, nuts and beer, and high in lysine-rich foods such as baked beans and eggs.

A small pilot study examined the use of a topical preparation SuperLysine Plus+ cream containing lysine plus other nutrients (zinc oxide, vitamins A, D, E, and lithium carbonate 3X) and botanicals (extracts of propolis, calendula, echinacea and goldenseal) in relieving the symptoms of herpes simplex. Patients with signs and symptoms of an active cold sore of less than 24 hours duration applied the ointment to the lesions 2-hourly during waking hours. Symptoms including severity of tingling, burning, and tenderness showed significant improvement by day 3 except oozing, and 40% of patients had full resolution; 87% of patients had full resolution after day 6 (Singh et al 2005).

OTHER USES

Osteoporosis prevention

Two studies have investigated the effects of oral L-lysine supplementation on calcium use to determine whether L-lysine has a role in the prevention of osteoporosis. In these tests, oral L-lysine was shown to significantly increase intestinal absorption of calcium and decrease renal excretion in both healthy women and those with osteoporosis (Civitelli et al 1992).

Anxiety and mood disturbances

According to a randomised, double-blind trial, fortification of lysine in a wheat-based (L-lysine deficient) diet significantly reduced anxiety score in males, but not females with high baseline anxiety. It is suspected that L-lysine's action as a 5-HT_4 receptor antagonist and benzodiazepine receptor agonist are responsible for the observed effect (Smriga et al 2004). In a recent double blind, randomised placebo-controlled study, Smriga et al (2007) evaluated the efficacy of combined lysine and arginine supplementation on reducing anxiety and stress response hormonal levels. Patients were given 1.32 g each of L-lysine and L-arginine twice daily for 1 week, estimated to be a 50% increase in total intake. Compared to placebo, long-term and stress-induced anxiety levels were reduced in both genders in the treatment group, and basal levels of salivary cortisol and chromogranin-A (a measure of sympathetic stress response) were significantly reduced in males (Smriga et al 2007). In contrast, a prospective study of 29,133 men (aged 50–69 years) found no association between L-lysine intake and depressed mood (Hakkarainen et al 2003).

Cancer treatment (in combination)

A formulation of lysine combined with other compounds (proline, arginine, vitamin C and green tea extract) has been used in several in vitro and in vivo studies suggesting it may be beneficial in cancer treatment by inhibiting growth, invasion and metastasis of tumour cells via inhibiting metalloproteinases which trigger excellular matrix degradation (Roomi et al 2004, 2005a–e, 2006a–e; Roomi 2006). In contrast to this, however, an in vivo study conducted on mice found L-lysine and vitamin C Lysin C Drink®, alone or in combination with epigallocatechin-gallate (EGCG) and amino acids Epican forte®, was not effective as a prophylactic or treatment in reducing primary tumour growth (neuroblastoma model) or in preventing metastases (Lode et al 2008).

Lysinuric protein intolerance (LPI)

LPI is an autosomal recessive transport disorder of the cationic amino acids which leads to decreased intestinal absorption and excessive renal loss of lysine, arginine and ornithine. Usual treatment involves restriction of protein and citrulline supplementation, which corrects many side effects except those related to lysine deficiency. Long-term low dose lysine supplementation improves plasma lysine concentration in patients and may help correct chronic lysine deficiency without causing side effects such as hyperammonaemia (Tanner et al 2007).

DOSAGE RANGE

Herpes simplex infections

- Prevention: 1000–3000 mg/day.
- Acute treatment: minimum 3000 mg/day in divided doses taken between meals until lesions have healed.

Osteoporosis prevention

- 400–800 mg L-lysine taken together with calcium supplementation.

TOXICITY

Not known.

ADVERSE REACTIONS

Doses greater than 10–15 g/day may cause gastrointestinal discomfort with symptoms of nausea, vomiting and diarrhoea.

SIGNIFICANT INTERACTIONS

Calcium

Clinical tests have found L-lysine enhances intestinal absorption and decreases renal excretion of calcium (Civitelli et al 1992) — potentially beneficial interaction.

PRACTICE POINTS/PATIENT COUNSELLING

- L-Lysine is an essential amino acid found in foods such as animal proteins, eggs and milk.
- It has been shown to inhibit HSV multiplication in vitro.
- Supplemental L-lysine is popular as a prophylactic and treatment for HSV.
- Studies have yielded inconsistent results suggesting that there may be individual variation in responses.
- Doses used as prophylaxis range from 1000–3000 mg/day with treatment doses generally above 3000 mg/day.
- L-Lysine may also enhance intestinal absorption of calcium and reduces its renal excretion.

CONTRAINDICATIONS AND PRECAUTIONS

Contraindicated in people with the rare genetic disorder hyperlysinaemia/hyperlysinuria (Hendler et al 2001). High-dose lysine supplements should be used with caution in hypercalcaemic states, and by people with kidney or liver disease.

PREGNANCY USE

Safety is unknown for high-dose supplements; however, dietary intake levels are safe.

PATIENTS' FAQs

What will this supplement do for me?

L-Lysine supplements may reduce the frequency and severity of herpes simplex outbreaks. It may also improve the way the body absorbs and retains calcium.

When will it start to work?

Studies suggest that several months' treatment may be required, with a long-term approach recommended.

Are there any safety issues?

L-Lysine appears to be a very safe supplement, although safety has not been established in pregnancy and lactation for high-dose supplements.

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Magnesium

HISTORICAL NOTE 'Magnesium' comes from the name of the ancient Greek city Magnesia, where large deposits of magnesium were found. In the form of Epsom salts, magnesium has long been used therapeutically as a laxative although it is also used in many other ways, such as a foot soak to soften rough spots and absorb foot odour and as a bath additive to ease muscle aches and pains.

BACKGROUND AND RELEVANT PHARMACOKINETICS

Magnesium (Mg) is the fourth most abundant cation in the body, with 50–60% sequestered in the bone, the remainder distributed equally between muscle and non-muscular soft tissue. Only about 1% of total body Mg is found in the extracellular fluid. Dietary intake, renal and intestinal function finely balance and maintain plasma Mg concentrations.

Absorption of dietary Mg starts within 1 h of ingestion, with salts of high solubility having the most complete absorption (e.g. magnesium citrate). Magnesium absorption requires selenium, parathyroid hormone and vitamins B_6 and D and is hindered by phytate, fibre, alcohol, excess saturated fat and the presence of unabsorbed fatty acids, high phosphorus or calcium intake (Johnson 2001, Saris et al 2000). However, calcium is no longer perceived to be as antagonistic to Mg uptake as previously thought, while research using test meals may show negative interaction — in contrast to long-term balance studies (Andon et al 1996, Fine et al 1991, Gropper et al 2009, Lewis et al 1989). Some authors suggest that such nutrient interactions only become significant in situations of low Mg intake (Gropper et al 2009, Lewis et al 1989). Healthy people absorb 30–40% of ingested Mg; increasing to 70% bioavailability in cases of low intake or deficiency (Braunwald et al 2003). Although currently it is undisputed that Mg metabolism is regulated, the identity of such regulators remains largely obscured (Gropper et al 2009). While a number of hormones affect magnesium homeostasis they fail to explain every facet. Our understanding is further complicated in light of magnesium's counter-control of these hormones.

While hormones central to calcium homeostasis, e.g. parathyroid hormone (PTH), play a role in Mg metabolism this is a greatly diminished one compared to calcium (Shils & Rude 1996). Additional regulators include adrenergic signalling pathways, insulin, oestrogen and growth hormone (Rude & Shils 2006). Some researchers suggest that the real locus of control over Mg homeostasis may be independent of hormones; instead a combination of fractional absorption, renal excretion and transmembranous cation flux (Gropper et al 2009).

Once absorbed, Mg travels to the liver, enters the systemic circulation and is transported around the body, to be ultimately excreted via the kidneys, with urine representing the major excretory pathway. Consequently, the kidney is pivotal in homeostatic control, rapidly adjusting to changing dietary intake (Rude & Shils 2006). Renal handling of Mg is subject to additional negative influences. For example, increased calcium (≈ 2600 mg/day) (NHMRC 2005), sodium, protein, caffeine and alcohol consumption (Gropper et al 2009, Rude & Shils 2006), B_6 depletion (Turnlund et al 1992), glycosuria (Khan et al 1999, Rude & Shils 2006, Turnlund et al 1992, Walti et al 2003), elevated thyroid hormones (Wester 1987) protein intakes either above or below recommended levels (Wester 1987) and increases in net endogenous acid production (Rylander et al 2006) — all impair the kidney's capacity to reabsorb magnesium. Additional minor losses occur through sweat and faeces (Gropper et al 2009, Rude & Shils 2006).

Magnesium assessment

In spite of intense ongoing research, there is still no simple, rapid and accurate laboratory test to determine total body Mg status in humans (Arnaud 2008, Feillet-Coudray et al 2000). In particular, as with many of the minerals, there is an urgent need to identify a functional or biological marker of Mg status, similar to the role of ferritin in iron assessment (Arnaud 2008). While serum testing is still frequently performed, it is only indicative of severe depletion, as evidenced by values < 0.75 mmol/L and while some studies demonstrate a correlation between these values and the Mg content of other tissues, many do not (Arnaud 2008). Some researchers suggest that serum values 0.75–0.85 mmol/L warrant further investigation with more sensitive tests.

Erythrocytes naturally contain large amounts of Mg and experimental depletion is reflected by declining RBC concentrations within weeks. A criticism of this method relates to repletion studies which found greater increases in serum Mg following supplementation than reflected in the RBC; however, one could argue that the diminished response is a more accurate reflection of delayed intracellular recovery. Both animal and human studies have shown Mg concentrations in white blood cells, e.g. lymphocytes, to be a particularly accurate indicator of Mg content of both skeletal and cardiac tissues, which, given their functional significance, represents an attractive option. Actual muscle biopsies are believed to be an excellent indicator of body status, however, due to their invasive nature, is rarely used (Arnaud 2008).

Increasingly, however, Mg loading tests are being considered the gold standard of Mg assessment (Arnaud 2008). The procedure involves either oral or IV loading with Mg (e.g. 500–700 mg) followed by collection of 24-h urine. Generally, excretion of < 70% is considered indicative of Mg deficiency. One of the significant disadvantages of this method is the lack of standardisation, e.g. form and dose of Mg administered, which is critical for ensuring

its sensitivity and reproducibility. Additionally, this test should only be used in individuals with healthy renal function generally and absorptive capacity, specifically, in oral loading.

FOOD SOURCES

Good dietary sources of Mg include legumes, wholegrain cereals, nuts, dark green leafy vegetables, cocoa, soy flour, seeds, nuts, mineral water and hard water.

DEFICIENCY SIGNS AND SYMPTOMS

When reduced intakes or increased losses of Mg, potassium or phosphorus occur (the three major intracellular elements), losses of the others generally follow. As such, many deficiency symptoms are also due to alterations in potassium and/or phosphorus status and manifest as neurological or neuromuscular symptoms.

Symptoms of deficiency include:

- anorexia and weight loss
- nausea and vomiting
- muscular weakness and spasms
- numbness, tingling, cramps
- spontaneous carpal–pedal spasm
- vertigo, ataxia, athetoid, chorioform movements
- lethargy
- difficulty remembering things
- apathy and melancholy
- confusion
- dysregulation of biorhythms (some sleep and mental health disorders including insomnia)
- depression
- mental confusion, decreased attention span and poor concentration
- personality changes
- hyper-irritability and excitability
- vertigo
- cardiac arrhythmia, tetany and ultimately convulsions can develop if deficiency is prolonged.

Although Mg deficiency is a common clinical problem, serum levels are often overlooked or not measured in patients at risk for the disorder. About 10% of patients admitted to hospitals and up to 65% of patients in intensive care units may be Mg deficient (Braunwald et al 2003).

Low Mg states are associated with several serious diseases such as congestive heart failure, ischaemic heart disease, cardiac arrhythmias, hypertension, mitral valve prolapse, metabolic syndrome, diabetes mellitus, hyperlipidaemia, pre-eclampsia and eclampsia (Fox et al 2001, Guerrero-Romero & Rodriguez-Moran 2002, Rude & Shils 2006). Epidemiological evidence suggests that a low dietary intake of Mg is also associated with impaired lung function, bronchial hyperreactivity and wheezing, and risk of stroke (Ascherio et al 1998, Hill et al 1997). Magnesium deficiency may also play a role in the pathophysiology of Tourette's syndrome (Grimaldi 2002).

Primary deficiency

A primary deficiency is rare in healthy people as the kidneys are extremely efficient at maintaining Mg homeostasis. Studies of experimental Mg depletion demonstrate that it takes months of intentional Mg deprivation to induce a deficiency and even then, its presentation is 'vague' and idiosyncratic (Shils & Rude 1996, Wester 1987).

Marginal deficiencies are far more common and very often undiagnosed. There is evidence that daily Mg intake has declined substantially since the beginning of last century, with dietary surveys showing the average intake in Western countries is often below the recommended daily intake (RDI) (Ford & Mokdad 2003, Lukaski 2000, Rude & Shils 2006, Saris et al 2000).

Secondary deficiency

In contrast to the low rates of reported primary Mg deficiency, secondary deficiency is common in both the acute and chronically ill (Gropper et al 2009, Shils 1964). Most Mg deficiencies occur due to a combination of insufficient dietary intake and/or intestinal malabsorption and increased Mg depletion. There are many factors that predispose to deficiency and these are listed in the table below.

Medicines increasing risk of deficiency

Many pharmaceutical drugs have the potential to cause hypomagnesaemia.

MAIN ACTIONS

Magnesium plays an essential role in a wide range of fundamental biological reactions in the body. It is involved in over 300 essential enzymatic reactions and is necessary for every major biological process. It is especially important for those enzymes that use nucleotides as cofactors or substrates and plays a role in many processes that are of central importance in the biochemistry of each cell, particularly in energy metabolism. It is also required for many other important biological functions such as:

- nerve conduction
- regulation of vascular tone
- muscle activity
- amino acid and protein synthesis
- DNA synthesis and degradation
- immune function
- natural calcium antagonist.

Interaction with other nutrients

Magnesium is extremely important for the metabolism of calcium, potassium, phosphorus, zinc, copper, iron, sodium, lead, cadmium and the intracellular homeostasis and activation of thiamine (Johnson 2001). It acts as a calcium antagonist and positively interacts with nutrients such as potassium, phosphorus, vitamin B_6 and boron.

OTHER ACTIONS

In its macro form, oral inorganic Mg salts have a laxative and antacid activity and are practically insoluble in water.

CLINICAL USE

In practice, Mg is administered by various routes such as intramuscular injection and intravenous infusion. This review will focus only on oral Mg, as this is the form most commonly used by the general public, outside the hospital setting.

Risk Factors for Magnesium Depletion	
Dietary	Excessive intake of ethanol, salt, phosphoric acid (soft drinks), caffeine Protein-energy malnutrition. There is evidence that Mg balance remains positive despite < RDI intake as long as protein > 30 g/day
Endocrine disorders	Hyperaldosteronism Hyperparathyroidism with hypercalcaemia Hyperthyroidism Diabetes mellitus and glycosuria
Lifestyle	Profuse sweating Intense, prolonged stress
Gastrointestinal disorders (gastrointestinal tract [GIT] absorptive surface pathology or reduced transit time or increased upper GIT loss)	Coeliac disease Infections Inflammatory bowel diseases Malabsorption syndromes Pancreatitis Partial bowel obstruction Vomiting/diarrhoea
Elevated cortisol levels	Chronic stress Sleep deprivation Athletes and high frequency exercise
Pharmaceutical drugs	Aminoglycoside antibiotics Cisplatin Corticosteroids Cyclosporin Loop diuretics Tetracycline antibiotics
Renal	Metabolic disorders Acidosis Nephrotoxic drugs (e.g. cisplatin, cyclosporin)
Other	Hyperthermia Hypercatabolic states such as burns Phosphate depletion Potassium depletion Pregnancy Lactation (prolonged (>12 months) or excessive lactation) Excessive menstruation Long-term parenteral nutrition combined with loss of body fluids (e.g. diarrhoea) Parasitic infection (e.g. pinworms)

(From Braunwald et al 2003, Johnson 2001, McDermott et al 1991, Sanders et al 1999, Shils et al 1999)

Deficiency: treatment and prevention

Magnesium supplementation is traditionally used to correct deficiency states or avoid deficiency in people at increased risk, such as people with malabsorption syndromes and chronic alcoholics (Saris et al 2000). Low serum Mg levels < 0.7 mmol/L (1.8 mg/dL, 1.5 mEq/L) are indicative of Mg deficiency, although symptoms occur when serum Mg is < 0.5 mmol/L (1.2 mg/dL, 1.0 mEq/L) (Braunwald et al 2003).

Cardiovascular disease

A protective effect from hard water consumption, and in particular Mg intake from this source, against cardiovascular disease has been hypothesised for many years, culminating in a meta-analysis which determined a pooled odds ratio of 0.75 for cardiovascular mortality (Catling et al 2008), although not all studies on this topic concur with these findings (Morris et al 2008). Additional epidemiological evidence continues to strongly link Mg deficiency to numerous cardiovascular disease (CVD) presentations (Alon et al 2006, Flight & Clifton 2006, Gropper et al 2009, Haenni et al 1998, Klevay & Milne 2002, Ma et al 1995, Rude & Shils 2006, Song et al 2006) including congestive heart failure, ischaemic heart disease, cardiac arrhythmias, hypertension, mitral valve prolapse, stroke, non-occlusive myocardial infarction and hyperlipidaemia (Fox et al 2001, Frishman et al 2005, Guerrero-Romero & Rodriguez-Moran 2002, Rasmussen et al 1988, Saris et al 2000).

Although the pathophysiology of each condition is multifactorial, the multiple biological effects of Mg in the cardiovascular system suggest an important cardioprotective role. In the heart, Mg acts as a calcium-channel blocker and promotes resting polarisation of the cell membrane, thereby

reducing arrhythmias (Shattock et al 1987). It also helps to prevent serum coagulation (Frishman et al 2005). Low Mg selectively impairs the release of NO from the coronary endothelium, resulting in vasoconstriction and possibly coronary embolism. Mg plays a role in blood lipid levels with detrimental changes, e.g. increased oxidation of LDLs, as well as generally increased oxidation, evident in hypomagnesaemia (Rude & Shils 2006). In experimental animals, dietary Mg deficiency exacerbates atherosclerosis and vascular damage because it has a modulatory role in controlling lipid metabolism in the arterial wall.

Mitral valve prolapse

It has been suggested that hypomagnesaemia is common in patients with mitral valve prolapse and therefore supplementation to correct this deficiency could exert beneficial clinical effects (Kitlinski et al 2004). In 1997, one study of 141 subjects with symptomatic mitral valve prolapse confirmed this suspicion by identifying hypomagnesaemia in 60% of patients (Lichodziejewska et al 1997). A randomised, double-blind, crossover study followed those Mg-deficient people and found that 5 weeks' Mg supplementation significantly alleviated symptoms of weakness, chest pain, dyspnoea, palpitation and anxiety (Lichodziejewska et al 1997). The dose regimen used was three tablets of magnesium carbonate 600 mg (7 mmol elementary Mg) daily for the first week followed by two tablets daily until the fifth week.

Symptoms of coronary artery disease (CAD)

In 2003, the results from a multicentre, multinational, prospective, randomised, double-blind and placebo-controlled trial showed that 6 months' oral Mg supplementation in patients with CAD results in a significant improvement in exercise tolerance, exercise-induced chest pain, and quality of life (QOL) (Shechter et al 2003). The study used oral magnesium citrate (15 mmol twice daily) as Magnosolv-Granulat (total Mg 365 mg). Previously, randomised placebo-controlled studies have shown that oral Mg supplementation in CAD patients is associated with significant improvement in brachial artery endothelial function and inhibits platelet-dependent thrombosis, providing several potential mechanisms by which Mg could beneficially alter outcomes in these patients (Shechter et al 1999, 2000).

Hypertension

Epidemiological evidence suggests an inverse relationship between blood pressure and serum Mg while large well-designed prospective studies report that Mg-rich diets may lower blood pressure, particularly in older individuals (Sontia & Touryz 2007). Magnesium modulates vascular tone and reactivity both directly, e.g. calcium-channel blocker, and indirectly, e.g. prostacyclin, and alters vascular responsivity to vasoactive agonists. However, Mg deficiency does not appear universal amongst hypertensive patients and several sub-groups have been identified as characteristically demonstrating both pathologies. These include individuals of African descent, obese patients, patients with severe or malignant presentations and those also diagnosed with metabolic syndrome.

This may partly explain the mixed findings produced from Mg supplementation studies, as well as additional heterogeneities in study designs such as the salts used, dose administered, sample size and trial duration (Sontia & Touryz 2007). Modest but significant success (≈ -2 to 5 mmHg), however, has been achieved particularly in those patients deficient at baseline, black individuals and those patients with diuretic-associated hypertension (Rude & Shils 2006, Sontia & Touryz 2007, Witteman et al 1994).

Stroke

A prospective study of 43,738 men (Health Professional Follow-up Study) conducted over 8 years showed an inverse association between dietary Mg intake and the risk of total stroke (Ascherio et al 1998). This association was stronger in hypertensive than normotensive men and was not materially altered by adjustments for blood pressure levels. A study has confirmed that this protective effect is maintained in male smokers (Larsson et al 2008). Following adjustment for age and other cardiovascular risks, high Mg intake was associated with a statistically significant reduced risk of cerebral infarct, with a relative risk of 0.85 across men of all ages or 0.76 in those men aged < 60 years, while the dietary intake of other minerals did not appear to convey any protection. At the other end of the spectrum, it is interesting to note that low concentrations of Mg in the serum or cerebrospinal fluid in acute ischaemic stroke patients at admission or within 48 hours of onset of the stroke predicts both greater neurological deficits, e.g. paresis, and higher 1 week mortality (Bayir et al 2009, Cojocaru et al 2007).

Dyslipidaemia

Oral Mg supplementation (magnesium oxide 12 mmol/day) taken over 3 months effectively reduced plasma lipids compared with placebo in people with ischaemic heart disease (Rasmussen et al 1989). The double-blind study showed that Mg produced a statistically significant 13% increase in molar ratio of apolipoprotein A1:apolipoprotein B compared with a 2% increase in the placebo group. This was caused by a decrease in apolipoprotein B concentrations, which were reduced by 15% in the Mg group as compared with a slight increase in the placebo group. Additionally, triglyceride levels decreased by 27% after Mg treatment. Overall, these beneficial results are associated with a decrease in cardiovascular mortality.

Arrhythmia prevention in congestive heart failure

Although Mg is usually administered intravenously when indicated in this condition, one controlled study using oral Mg showed that it significantly reduced the incidence of arrhythmias in patients with stable congestive heart failure (Bashir et al 1993). The double-blind crossover study used magnesium chloride (3204 mg/day in divided doses).

Postoperative recovery from cardiac surgery

An interesting Australian study employed a range of preoperative treatments addressing mental, physical and metabolic components, including magnesium. The results of this preliminary study, using 1200 mg magnesium orotate, together with 300 mg CoQ10, 300 mg alpha-lipoic acid and 3 g omega-3 essential fatty acids (EFAs) administered daily 1 month prior to surgery, suggest an enhanced postoperative recovery and improved quality of life (Hadj et al 2006). IV administration of Mg sulfate is also used to reduce the risk of atrial fibrillation postsurgery (Burgess et al 2006).

Calcium and hormone replacement therapy (HRT): a deadly mix in postmenopausal women?

The failure of oestrogen replacement therapy to protect against cardiovascular disease in the Women's Health Initiative (WHI) Study has provoked much reflection amongst researchers. One theory pertains to oestrogen's role in Mg homeostasis and Mg's antagonism of calcium (Seelig et al 2004). In high oestrogen states, Mg uptake by tissues is stimulated (Seelig et al 1993). In scenarios of inadequate Mg, however, this action results in low serum Mg concentrations and in particular an increased ratio of serum calcium to magnesium. This in turn promotes a pro-thrombotic environment, as a result of calcium's promotion of the coagulation cascade and vasoconstrictive effects. The group of researchers supporting this theory points to the promotion of a high calcium diet and/or calcium supplementation in postmenopausal women, in the face of inadequate Mg consumption, as being behind the increased vascular events (particularly of a thromboembolic nature) evident in the WHI and other calcium supplementation studies in postmenopausal women (Bolland et al 2008).

Migraine headaches: prevention

People who suffer with recurrent migraines appear to have lower intracellular Mg levels (demonstrated in both red and white blood cells) than those who do not experience migraines. (See 'Feverfew' monograph for more information about migraine aetiology.) The low Mg level is believed to result in cerebral artery spasm and increased release of substance P and other pain mediators (Woolhouse 2005).

Two randomised, double-blind studies using high-dose oral Mg have found it to be useful in migraine sufferers, reducing frequency and/or number of days with migraine headache (Peikert et al 1996, Taubert 1994). One placebo-controlled study using a lower dose found no benefit in reducing the frequency of migraine headaches (Pfaffenrath et al 1996).

A dose of 24 mmol Mg (600 mg trimagnesium dicitrate) taken daily over 12 weeks produced a 42% reduction in frequency of attack compared with 16% with placebo in one study of 81 patients, with a mean attack frequency of 3.6 migraine headaches each month (Peikert et al 1996). Effects were observed after week 9 and treatment also significantly decreased the duration of each migraine. Significant decreases in migraine frequency were also observed in a crossover study that used the same dose and form of oral Mg (Taubert 1994).

Menstrual migraine headache

Oral Mg supplementation decreases pain, premenstrual symptoms and the number of days with migraine headache, according to one double-blind placebo-controlled study (Facchinetti et al 1991a). Treatment consisted of 360 mg/day of Mg (pyrrolidone carboxylic acid) starting on day 15 of the menstrual cycle and continuing until the onset of menses.

Migraine prophylaxis in children

Oral magnesium oxide (9 mg/kg/day) given in three divided doses with food may decrease headache frequency and severity according to a multicentre, randomised, double-blind, placebo-controlled trial (Wang et al 2003). The 16-week study involved children aged 3–17 years who reported a 4-week history of at least weekly, moderate-to-severe headache with a throbbing or pulsatile quality, associated anorexia/nausea, vomiting, photophobia, sonophobia or relief with sleep, but no fever or evidence of infection. Of note, 27% of subjects (n = 42 magnesium oxide; n = 44 placebo) failed to complete the study, thereby hindering interpretation of the results.

Attention deficit and hyperactivity disorder (ADHD)

Several studies have demonstrated a positive correlation between Mg status and ADHD pathology. Reported prevalence of hypomagnesaemia varies between 50% and 95% (Kozielec & Starobrat-Hermelin 1997, Mousain-Bosc et al 2004) A hypothesised genetic mutation involves the TRPM6 gene which is crucial for Mg transport and homeostasis, therefore making deficiency possible irrespective of adequate intake (Mousain-Bosc et al 2004). There have been two Mg supplementation studies in combination with vitamin B_6 (6 mg/kg/

Clinical note — What is the link between magnesium and migraine?

Magnesium seems to play a significant role in the pathogenesis of migraine, with low brain levels and impaired Mg metabolism reported in migraine sufferers (Thomas et al 2000). Magnesium has an effect on serotonin receptors, NO synthesis and release and a variety of other migraine-related receptors and neurotransmitters. It is also essential for mitochondrial function within the cell. The available evidence suggests that up to 50% of patients during an acute migraine attack have lowered levels of ionised Mg (Mauskop & Altura 1998). Pilot studies of migraine patients have suggested that disordered energy metabolism or Mg deficiencies may be responsible for hyperexcitability of neuronal tissue in migraine patients (Boska et al 2002). As such, factors that decrease neuronal excitability, such as Mg, may alter the threshold for triggering attacks (Boska et al 2002).

day ± 0.6–0.8 mg/kg/day vitamin B_6) (Mousain-Bosc et al 2004), with both producing significant behavioural improvement.

Autism spectrum disorders (ASD)

Research suggests that ASD sufferers generally demonstrate red blood cell Mg depletion (Mousain-Bosc et al 2006, Strambi et al 2006). In spite of two negative reviews published 10 years apart (Nye & Brice 2005, Pfeiffer et al 1995), enthusiasm regarding the use of Mg as an adjunct to high-dose vitamin B_6 therapy (6 mg/kg/day with 0.6–0.8 mg/kg/day vitamin B_6) (Kidd 2002, Mousain-Bosc et al 2006) in ASD continues. This may ultimately prove successful given the limited trials, poor methodological rigour to date (Nye & Brice 2005, Pfeiffer et al 1995) and preliminary evidence from two small successful trials (Kidd 2002).

Kidney stone prevention

Magnesium deficiency is one of many risk factors for the development of kidney stones (Anderson 2002). Others include nutritional deficiencies of water, calcium, potassium and vitamin B_6, excessive intakes of animal protein, fat, sugar, oxalates, colas, alcohol, caffeine, salt and vitamin D, lifestyle factors and a positive family history.

A prospective double-blind study of 64 patients who were randomly assigned to receive placebo or potassium–magnesium citrate (42 mEq potassium, 21 mEq magnesium and 63 mEq citrate) daily for up to 3 years showed that the combination supplement reduced the risk of developing recurrent calcium oxalate kidney stones by 85% (Ettinger et al 1997).

Premenstrual syndrome (PMS)

Three early double-blind studies using oral Mg supplements in women with PMS produced positive results for decreasing symptoms such as fluid retention and mood swings (Facchinetti et al 1991b, Rosenstein et al 1994, Walker et al 1998). According to these, clinical effects develop slowly, starting during the second menstrual cycle.

Although it is not clear what mechanism of action is responsible, a number of studies have identified decreased Mg concentrations in both red blood cell and mononuclear blood cells of women with PMS (Rosenstein et al 1994) and therefore the suggestion is that the clinical benefits were secondary to repletion. The results of a more recent study strongly challenge these earlier findings (Khine et al 2006). The Mg status of 17 PMS patients and 14 age-matched controls was comprehensively assessed using four different techniques: serum, red blood cell and mononuclear blood cell concentrations, together with a Mg loading test. The results failed to demonstrate a relationship between Mg status and the diagnosis or severity of PMS. In addition to this, while subsequent Mg treatment in PMS patients produced robust reductions in symptom ratings, these were highly comparable with the placebo response. The latter throws speculation upon the positive results of open label studies of Mg in PMS, such as the 35% reduction in symptoms demonstrated after 3 months treatment with Mg 250 mg/day, demonstrated by Quaranta et al (2007).

Dysmenorrhoea

A Cochrane review of seven randomised trials investigating the effects of various treatments for dysmenorrhoea included three trials comparing Mg with placebo. Overall, Mg was found to be more effective than placebo for pain relief and resulted in less extra medication being required (Wilson & Murphy 2001).

Osteoporosis prevention

Magnesium comprises about 1% of bone mineral and is involved in a number of activities supporting bone strength, preservation, and remodelling. Epidemiological studies have linked increased Mg consumption, as part of an alkaline diet, with improved bone mineral density (Tucker et al 1999). Chronic Mg deficiency compromises bone health by increasing the size and brittleness of the bone crystals, inducing hypocalcaemia and possibly increasing inflammatory cytokines (Rude & Shils 2006). Therefore, low Mg states increase the risk of osteoporosis. Several studies have investigated the effects of supplemental Mg on bone density, generally yielding positive effects.

One long-term study has reported an increase in bone density for magnesium hydroxide supplementation in a group of menopausal women (Sojka & Weaver 1995). After the 2-year test period, fracture incidence was also reduced. Another 2-year study showed that Mg supplementation in postmenopausal women with osteoporosis results in increased bone mass at the wrist after 1 year, with no further increase after 2 years of supplementation (Stendig-Lindberg et al 1993). The regimen used here was oral Mg 750 mg/day for the first 6 months followed by 250 mg/day thereafter.

Asthma

There is ongoing evidence of low intracellular (both red and white blood cells) Mg in asthmatics in some (Dominguez et al 1998, Mircetic et al 2001, Sedighi et al 2006) but not all studies. Healthy Mg concentrations inhibit calcium entering smooth muscles such as those in the airways and therefore potentially reduce bronchospasm (Dominguez et al 1998, Gropper et al 2009). In addition to this, Mg influences pulmonary vascular muscle contractility, mast-cell granulation and neurohumoral

> ***Clinical note — Peak bone mass***
> The best opportunity to influence bone mass occurs early in life. It has been estimated that approximately 40% of peak bone mass is accumulated during adolescence with peak bone mass in the hip achieved by age 16–18 years (Weaver 2000). The spinal vertebrae are still able to increase in mass until the third decade of life, when total peak bone mass reaches 99% by age 26.6 years (± 3.7 years). As such, ensuring an adequate intake of calcium and Mg early in life is essential for attaining optimal bone mass.

mediator release (Mathew & Altura 1988). Although it is most often used as an infusion or in an inhaled form for this indication, results of two randomised, double-blind studies suggest that oral supplements also significantly alleviate asthma symptoms (Bede et al 2003, Hill et al 1997). Hill et al found that treatment improved symptoms, although it failed to change objective measures of airflow or airway reactivity and Bede et al found a significant decrease in bronchodilator use after 8 weeks compared with placebo. This was a 12-week study using oral magnesium citrate in 89 children (4–16 years) with mild or moderate persistent bronchial asthma. The dose used was 200 mg daily for children aged 7 years and 290 mg for those older than 7 years. Adding to this, a randomised double-blind trial of magnesium glycine (300 mg/day) in 37 subjects aged 7–19 years over 2 months resulted in statistically significant reduction in bronchial reactivity, skin responses to recognised antigens and salbutamol use in the treatment versus the placebo group (Gontijo-Amaral et al 2007).

Pregnancy

A 2001 Cochrane review of seven studies involving 2689 women concluded that although not all trials were positive, oral Mg taken before the 25th week of gestation was associated with a lower frequency of preterm birth, a lower frequency of low birthweight and fewer small-for-gestational-age infants.

Additionally, fewer hospitalisations during pregnancy and fewer cases of antepartum haemorrhage were associated with Mg use.

Unfortunately, a lack of high-quality evidence precludes conclusively stating that dietary Mg supplementation during pregnancy is beneficial, according to the authors, with further research still required to confirm these findings (Makrides & Crowther 2001).

Pre-eclampsia

While a consistent relationship between Mg status and risk of pre-eclampsia has not been established, an interesting longitudinal study revealed that while serum Mg levels decline in both healthy and pre-eclamptic pregnant women, such a decrease occurs earlier in those women who later develop this condition (Sontia & Touryz 2007).

Pregnancy-induced leg cramps

A 2002 Cochrane review of five randomised trials of treatments for leg cramps in pregnancy concluded that the best evidence is for magnesium lactate or citrate taken as 5 mmol in the morning and 10 mmol in the evening for pregnant women experiencing leg cramps (Young & Jewell 2002).

Diabetes mellitus

A strong association between Mg, diabetes and hypertension has been reported in the literature (Ascherio et al 1998, Sontia & Touryz 2007). Deficiency aggravates insulin resistance and predisposes diabetics to cardiovascular diseases.

Type 1 diabetes mellitus (T1DM)

Hypomagnesaemia is present in 25–38% of all diabetic patients secondary to glycosuria and Mg redistribution (Paolisso et al 1992). Such depletion may occur early in the pathology, with T1DM children demonstrating progressive deterioration of serum levels within 2 years of diagnosis in some (Tuvemo et al 1997) but not all studies (Matthieson et al 2004). Magnesium depletion in T1DM has also been linked to earlier atherosclerotic development (Atabek et al 2006, Djurhuus et al 1999), polyneuropathy (De Leeuw et al 2004), advanced retinopathy (de Valk et al 1999) and immunosuppression (Cojocaru et al 2006). Supplementation studies have produced mixed results (Eibl et al 1998); however, Mg supplementation may reduce risks of secondary pathology.

Consistent with these findings, some researchers suggest T1DM patients receive a high dose in the first month of treatment to normalise red blood cell and serum Mg and then remain on continuous lower dose supplementation (e.g. 300 mg/day) in order to avoid a return to hypomagnesaemia (Eibl et al 1998).

Type 2 diabetes mellitus (T2DM)

Epidemiological studies have drawn a link between poor dietary and/or serum Mg and an increased risk of T2DM (Chambers et al 2006, He et al 2006, van Dam et al 2006). In one large study those in the lowest tertile of Mg and fibre intakes exhibited a 3–4 times greater risk (Bo et al 2006). Serum Mg depletion is also evident in ≈ 25–38% patients. Hypomagnesaemia in diabetic patients appears to exacerbate impaired insulin resistance, elevated fasting blood glucose and HbA_{1c} concentrations (He et al 2006, Walti et al 2003). Oral Mg (magnesium chloride 2.5 g/day for 4 months) adjunctive to hypoglycaemic medication has produced reductions of fasting glucose (−37.5%), HbA_{1c} (−30.4%), and homeostasis model assessment (HOMA)-IR index (−9.5%) and insulin (Rodriguez-Moran & Guerrero-Romero 2003), while other studies demonstrate increased insulin levels with improved action (Paolisso et al 1992). In another study, a combination of Mg (200 mg/day), zinc (30 mg/day) and vitamins (C 200 mg/day and E 150 mg/day) over 3 months significantly increased levels of HDL and apo-A1 24% and 8.8%, respectively (Farvid et al 2004).

Several randomised studies investigating oral Mg supplementation have shown improvements in diabetic control (Paolisso et al 1992, Rodriguez-Moran & Guerrero-Romero 2003). A double-blind trial that involved 63 patients with type 2 diabetes (treated with glibenclamide) and reduced serum Mg levels demonstrated that the addition of oral Mg over 16 weeks significantly improves insulin sensitivity and metabolic control (Rodriguez-Moran & Guerrero-Romero 2003).

Constipation

In high doses Mg exerts a laxative effect, which is used in practice for the short-term treatment of constipation and in order to get the bowel ready for

Clinical note — Magnesium citrate and orotate: superior supplements?

Magnesium supplements come in a variety of salts (citrate, oxide, gluconate, acetate, orotate, etc.), however their bioavailability varies. Current evidence, although not clearly demonstrating superiority of one preparation over another, supports the use in general of organic over inorganic forms (Coudray et al 2005, Firoz & Graber 2001, Lindberg et al 1990, Walker 2003). In particular, investigations of magnesium orotate (Lindberg et al 1990), citrate (Walker 2003) and gluconate (Coudray et al 2005) demonstrate high solubility and bioavailability. Magnesium orotate has attracted further attention regarding its potential synergism with magnesium in terms of repair of damaged myocardium (Classen 2004, Zeana 1999).

According to one randomised, double-blind, placebo-controlled study, magnesium amino chelate and magnesium citrate are better absorbed than magnesium oxide in healthy individuals (Walker et al 2003). Of the three, magnesium citrate led to the greatest increase in mean serum Mg, a result evident after acute dosing (24 h) and chronic dosing (60 days). Furthermore, although mean erythrocyte Mg concentration showed no differences among groups, chronic magnesium citrate supplementation resulted in the greatest mean salivary Mg concentration compared with all other treatments.

surgical or diagnostic procedures. It is often used in the form of magnesium hydroxide (milk of magnesia) or magnesium sulfate (Epsom salts).

Dyspepsia

As magnesium hydroxide (milk of magnesia), Mg is used to reduce symptoms of dyspepsia and gastric acidity and acts as an antacid by forming magnesium chloride in the stomach. Magnesium oxide is also used for its antacid properties, which are greater than magnesium carbonate and sodium bicarbonate (Reynolds et al 1982). Magnesium trisilicate is the form used when a prolonged antacid activity is required.

Chronic leg cramps

Two randomised, double-blind studies have investigated the use of oral Mg supplements in people with leg cramps. Frusso et al (1999) conducted a crossover trial involving 45 individuals who had experienced at least six cramps during the previous month. Subjects were given 1 month of oral magnesium citrate (900 mg twice daily) followed by a matching placebo for 1 month, or visa versa. This treatment regimen failed to reduce the severity, duration or number of nocturnal leg cramps. In contrast, Roffe et al (2002) tested magnesium citrate equivalent to 300 mg magnesium in subjects suffering regular leg cramps and identified a trend towards fewer cramps with active treatment (P = 0.07). Significantly more subjects thought that the treatment had helped after magnesium than after placebo — 36 (78%) and 25 (54%) respectively. Interestingly, in both studies patients improved over time regardless of the treatment they received.

Although two additional studies in athletes found no correlation between cramping incidence and serum Mg, the authors suggest that the cramping was caused by increased neuromuscular excitability (Schwellnus et al 2004, Sulzer et al 2005), which is a classic feature of Mg deficiency (Rude & Shils 2006). As is the case with much Mg research, more accurate and validated assessment methods may be required to elicit the true relationship between Mg status and this presentation.

OTHER USES

Oral Mg supplements are used in a variety of different conditions, most notably those involving muscle spasm or tension, pain and/or psychological and physical symptoms of stress and hyperexcitability. This includes irritable bowel syndrome (IBS), restless legs syndrome, fibromyalgia, chronic fatigue syndrome, anxiety states, tension headaches and insomnia. Preliminary evidence also suggests that it may be beneficial for women with detrusor muscle instability (incontinence) or sensory urgency.

DOSAGE RANGE

Australian RDI for adults

- Men
  - 19–30 years: 400 mg/day.
  - > 30 years: 420 mg/day.
- Women
  - 19–30 years: 310 mg/day.
  - > 30 years: 320 mg/day.
- Pregnancy
  - ≤ 18 years: 400 mg/day.
  - > 18 years: 350 mg/day.
- Lactation
  - ≤ 18 years: 360 mg/day.
  - > 18 years: 310 mg/day.

According to clinical studies

- Hypertension: 360–600 mg/day.
- Arrhythmia prevention in congestive heart failure: magnesium chloride 3204 mg/day in divided doses.
- Migraine: 600 mg trimagnesium dicitrate daily.
- Migraine prophylaxis in children: magnesium oxide (9 mg/kg/day).
- PMS fluid retention symptoms: 200 mg magnesium (as magnesium oxide) daily.
- PMS mood swings: magnesium pyrrolidone carboxylic acid (360 mg) taken three times daily, from day 15 of the menstrual cycle to the onset of menstrual flow.
- Mitral valve prolapse: three tablets magnesium carbonate 600 mg (7 mmol of elementary Mg) daily for the first week followed by two tablets daily.
- CAD symptoms: oral magnesium citrate (15 mmol twice daily as Magnosolv-Granulat, total magnesium 365 mg).
- Postoperative recovery from cardiac surgery: 1200 mg magnesium orotate in combination with 300 mg CoQ10, 300 mg alpha-lipoic acid and 3 g omega-3 oils taken daily 1 month prior to surgery.

- T1DM: initial high dose to normalise serum levels and then continuous 300 mg daily.
- T2DM: 2.5 g magnesium dichloride daily or 300 mg elemental Mg in combination with 30 mg zinc, 250 mg vitamin C and 150 mg vitamin E daily.
- ADHD: 6 mg/kg/day ± 0.6–0.8 mg/kg/day vitamin B_6.
- ASD: 6 mg/kg/day ± 0.6–0.8 mg/kg/day vitamin B_6.
- Kidney stone prevention: magnesium hydroxide 400–500 mg/day.
- Nocturnal leg cramps: magnesium citrate equivalent to 300 mg magnesium daily.
- Paediatric asthma: magnesium citrate 200–300 mg daily.
- Osteoporosis prevention: 250 mg taken at bedtime on an empty stomach, increased to 250 mg three times daily for 6 months, followed by 250 mg/day for 18 months.

ADVERSE REACTIONS

The most common adverse effects of oral supplements are diarrhoea (18.6%) and gastric irritation (4.7%) (Peikert et al 1996). Typically, doses of inorganic preparations supplying above 350 mg/day (elemental) may be associated with adverse effects. Dividing total daily supplemental amounts over 2–3 separate doses may help to reduce this risk and maximise bioavailbility.

SIGNIFICANT INTERACTIONS

The interactions included in this section are relevant for oral supplementation and do not refer to other administration routes, although there may be an overlap.

Alcohol

Alcohol consumption results in increased urinary losses of Mg and therefore with higher chronic ingestion additional Mg replacement may be necessary.

Aminoglycosides (e.g. gentamycin)

Drug may reduce absorption of Mg — monitor for signs and symptoms of Mg deficiency, as increased Mg intake may be required with long-term therapy.

Anti-arrhythmic drugs

Additive effect theoretically possible because high-dose oral Mg exerts anti-arrhythmic activity according to one clinical study — observe patients taking this combination.

Calcium

Magnesium and calcium deficiencies usually co-exist due to magnesium's key role in active PTH and vitamin D production (Gropper et al 2009, Rude & Shils 2006, Wester 1987). Conversely, if Mg intakes are excessive calcium levels decline due to inhibition of PTH release and increased renal excretion. There is additional redistribution with impaired calcium influx and release from intracellular stores. Magnesium can also bind calcium-binding sites and mimic its actions (Gropper et al 2009, Rude & Shils 2006).

Calcium-channel blockers

Magnesium may enhance the hypotensive effect of calcium-channel blockers: monitor patients and their drug requirements — possible beneficial interaction.

Fluoroquinolones

Magnesium may decrease absorption of fluoroquinolone antibiotics — separate doses by at least 2 h before or 4 h after oral Mg.

Loop diuretics and thiazide diuretics

Increased Mg intake may be required with long-term therapy because these drugs increase Mg loss — monitor Mg efficacy and status with long-term drug use.

Potassium

Hypomagnesaemia results in hypokalaemia due to increased potassium efflux from cells and renal excretion (Gropper et al 2009, Rude & Shils 2006).

Potassium-sparing diuretics

May increase the effects of supplemental Mg — observe patients taking this combination.

Tetracycline antibiotics

Tetracyclines form insoluble complexes with Mg, thereby reducing absorption of both — separate doses by at least 2 h.

CONTRAINDICATIONS AND PRECAUTIONS

- Magnesium supplementation is contraindicated in renal failure and heart block (unless a pacemaker is present).
- Hypermagnesaemia can develop in patients with renal failure and receiving Mg-containing antacids or laxatives and with accidental Epsom salt ingestion.
- Overuse of magnesium hydroxide or magnesium sulfate may cause deficiencies of other minerals or lead to toxicity.

PREGNANCY USE

Pregnant women and nursing mothers are advised to consume sufficient Mg (see Australian RDI under *Dosage range*).

PATIENTS' FAQs

What will this supplement do for me?

Magnesium is essential for health and wellbeing. Although used to prevent or treat deficiency states, it is also used to alleviate many conditions such as cardiovascular disease and PMS, and prevent migraine and muscular spasms.

When will it start to work?

This will depend on the indication it is being used to treat.

Are there any safety issues?

In high doses, supplements can cause diarrhoea. High-dose supplements should not be used by people with severe kidney disease or heart block.

PRACTICE POINTS/PATIENT COUNSELLING

- Magnesium is an essential mineral in human nutrition with a wide range of biological functions.
- Low Mg states are associated with several serious diseases such as congestive heart failure, ischaemic heart disease, cardiac arrhythmias, hypertension, mitral valve prolapse, metabolic syndrome, stroke, diabetes mellitus, hyperlipidaemia, pre-eclampsia and eclampsia.
- Although supplementation is traditionally used to correct or avoid deficiency states, research has also shown a role in the management of numerous disease states, e.g. asthma, cardiovascular disease, PMS, dysmenorrhoea, migraine prevention, diabetes, kidney stone prevention, osteoporosis prevention, dyspepsia and constipation. Preliminary research also suggests a possible benefit in ADHD, autism, women with detrusor muscle instability (incontinence) and pregnancy-induced leg cramps.
- Oral Mg supplements are also used in a variety of different conditions, most notably those involving muscle spasm or tension, pain and/or psychological and physical symptoms of stress and hyperexcitability.
- Numerous drug interactions exist, so care should be taken to ensure safe use.

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Meadowsweet

HISTORICAL NOTE Meadowsweet was one of the most sacred herbs used by ancient Celtic druid priests, hundreds of years ago (Blumenthal et al 2000). Modern-day aspirin owes its origins to the salicin content isolated from meadowsweet in the early 1800s. In fact, the name aspirin relates to this herb's former genus name 'Spiracea'.

COMMON NAME
Meadowsweet

OTHER NAMES
Bridewort, dolloff, dropwort, fleur d'ulmaire, gravel root, lady of the meadow, meadow-wort, queen of the meadow, spireae flos.

BOTANICAL NAME/FAMILY
Filipendula ulmaria (family Rosaceae)

PLANT PART USED
Aerial parts

CHEMICAL COMPONENTS
Phenolic glycosides, essential oil, tannins, mucilage, flavonoids (up to 6% in fresh flowers) and ascorbic acid. The herb also contains various salicylate constituents including methyl salicylate, salicin and salicylic acid.

MAIN ACTIONS

Gastroprotective effects
In vivo tests have identified protective effects against stomach ulcers induced by acetylsalicylic acid, but no protection was seen against ulcers produced under high-acid environments or due to stimulation by histamine (Barnaulov & Denisenko 1980). Based on these observations, it appears that the effect may involve a prostaglandin (PG)-mediated mechanism.

Hepatoprotective
An in vivo trial has demonstrated the hepatoprotective and antioxidant effects of meadowsweet (Shilova et al 2006). Meadowsweet extract (70% ethanol, 100 mg/kg) was shown to improve liver function in carbon tetrachloride (CCL4)-induced hepatitis in rats. In many parameters, the extract was shown to be more effective than Carsil, a silymarin preparation well known for its hepatoprotective ability.

OTHER ACTIONS
In vitro tests have identified antioxidant and anticoagulant activities (Calliste et al 2001, Liapina & Koval'chuk 1993). Bacteriostatic activity has also been reported in vitro against *Staphylococcus aureus*, *S. epidermidis*, *Escherichia coli*, *Proteus vulgaris* and *Pseudomonas aeruginosa* (Rauha et al 2000). Whether meadowsweet exerts anti-inflammatory and analgesic effects because of its

high salicylate content is unknown and remains to be tested.

CLINICAL USE

Meadowsweet has not been significantly investigated under clinical trial conditions, so evidence is largely derived from traditional, in vitro and animal studies.

Supportive therapy for colds

Commission E approval for this condition is based on historical use in well-established systems of medicine, in vitro tests and animal studies (Blumenthal et al 2000).

Acne

Researchers believe that Filipendula may stimulate the skin's natural immune mechanisms, reducing bacterial colonies and therefore limiting the complications of acne (Lenaers et al 2007). Volunteers used the Filipendula preparation twice a day for 28 days and found a reduction in acne spots by 10%, an improvement in the homogeneity of the skin grain by 21% and a reduction of inflammatory lesions by 20%. Bacterial infiltration of lesions was also reduced by 22%.

Gastrointestinal conditions

Meadowsweet is often used to treat gastrointestinal conditions associated with hyperacidity, such as gastritis, acidic dyspepsia and peptic ulceration. In vivo testing has found a decoction made from flowers of meadowsweet reduced experimentally induced ulcers caused by acetylsalicylic acid. Additionally, it promoted healing of chronic stomach ulcers induced by ethanol (Barnaulov & Denisenko 1980). Currently, there is no evidence available to confirm an antacid activity.

Conditions associated with mild-to-moderate pain

Based on its significant salicylate content, meadowsweet is also prescribed for conditions associated with mild-to-moderate pain. However, no clinical study is available to confirm efficacy.

OTHER USES

Meadowsweet has traditionally been used as a treatment for diarrhoea based on the herb's appreciable tannin content. It has also been used for conditions associated with mild-to-moderate pain (most likely due to the herb's significant salicylate content), fever and inflammation.

DOSAGE RANGE

As no clinical trials are available to determine effective doses, the following doses are a general guideline.

- Fresh flowers: 2.5–3.5 g/day.
- Fresh herb: 4–5 g/day.
- Infusion: steep 2–3 g in 150 mL boiled water for 10 min and drink as hot as tolerable.
- Fluid extract (1:1) (g/mL): 2–3 mL/day.

TOXICITY

Not known.

ADVERSE REACTIONS

Although salicylates are present, they appear to cause less gastrointestinal irritation than acetylsalicylic acid. In fact, a meadowsweet preparation protected against acetylsalicylic acid-induced stomach ulcers in vivo (Barnaulov & Denisenko 1980).

SIGNIFICANT INTERACTIONS

Controlled studies are not available; therefore, interactions are based on evidence of activity and are largely theoretical and speculative.

Aspirin and simple analgesics

Theoretically, meadowsweet may enhance anti-inflammatory and antiplatelet effects. Observe patients taking this combination — beneficial interaction possible.

Iron

Separate doses of iron and meadowsweet by 2 hours.

Warfarin

As increased bleeding may occur, observe patients taking warfarin concurrently. The herb has been shown to exert anticoagulant activity in vitro and in vivo, but the clinical significance of these results is unknown (Liapina & Koval'chuk 1993).

CONTRAINDICATIONS AND PRECAUTIONS

Meadowsweet should not be taken by people with salicylate sensitivity. Suspend use of concentrated extracts 1 week before major surgery.

PREGNANCY USE

Safety unknown.

PATIENTS' FAQs

What will this herb do for me?

Traditionally, the herb has been used to treat gastrointestinal complaints such as dyspepsia and diarrhoea, urinary tract infections and joint aches and

PRACTICE POINTS/PATIENT COUNSELLING

- Meadowsweet is traditionally used as a herbal antacid, analgesic and antipyretic, antidiarrhoeal and treatment for urinary tract infections.
- Commission E approves its use as supportive therapy for the common cold.
- It contains several different salicylates that are thought to be responsible for much of its clinical activity; however, this remains to be proven.
- Although it contains salicylates, the herb does not appear to cause significant gastrointestinal irritation and may, in fact, have anti-ulcer activity.
- People who are salicylate sensitive should not take this herbal medicine.
- In practice, it is often combined with herbs such as chamomile and marshmallow in the treatment of gastrointestinal complaints.

pains. It is also used as supportive therapy for the common cold.

When will it start to work?

Symptomatic relief should be experienced within the first few doses.

Are there any safety issues?

People who are salicylate sensitive should not take meadowsweet.

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Mullein

HISTORICAL NOTE Over the centuries, mullein has been used in various ways. Taken internally, it has been used to treat respiratory conditions and tumours; applied topically, its use has been to relieve itch and dress wounds. It was also used to make candlewicks for casting out evil spirits. Due to its robust nature, mullein is now considered a serious weed pest of roadsides and industrial areas in countries such as the USA.

OTHER NAMES

Aaron's rod, Adam's flannel, blanket herb, bunny's ears, candlewick plant, flannel-leaf, great mullein, Jacob's staff, flannelflower, gidar tamaku, hare's beard, hedge taper, longwort, Our Lady's flannel, rag paper, shepherd's club, shepherd's staff, torch weed, velvet plant, wild ice leaf, woollen, woolly mullein.

BOTANICAL NAME/FAMILY

Verbascum densiflorum, *Verbascum phlomoides*, *Verbascum thapsus* (family Scrophulariaceae)

PLANT PARTS USED

Flower — dried petals, leaves

CHEMICAL COMPONENTS

The flower contains water-soluble mucilage, polysaccharides, flavonoids (including apigenin, luteolin, kaempferol and rutin), caffeic acid derivatives, iridoid monoterpenes, triterpene saponins (verbascosaponin), sterols and invert sugar.

One of the most investigated constituents isolated from *Verbascum* spp. plants is verbascoside, an iridoid glucoside. Whether the pharmacological effects demonstrated for this single constituent can be extrapolated to explain those for mullein is uncertain, as the effects of any herb are due to a number of phyto-constituents and their interaction with each other and the body. As such, information about verbascoside is included here in order to provide a further insight into the herb, but it should be interpreted accordingly.

Verbascoside has also been isolated from other herbs such as *Verbena officinalis*, *Echinacea purpurea* roots, *Euphrasia pectinata*, *Phlomis longifolia*, *Pedicularis plicata*, *Duranta erecta*, *Marrubium alysson*, *Leonurus glaucescens* and *Ballota nigra* (Calis et al 1992a, b, Deepak & Handa 2000, Ersoz et al 2000, 2001, Liao et al 1999, Seidel et al 2000, Sloley et al 2001, Takeda et al 1995).

> ***Clinical note — Natural mucilages found in herbs***
>
> Mucilages are large, highly branched polymeric structures made from many different sugar and uronic acid units. They are hydrophilic and are capable of trapping water, causing them to swell in size and develop a gel-like consistency. The gels tend to have soothing properties and can be broken down by bowel flora when taken internally (Mills & Bone 2000). They are known to have beneficial effects on burns, wounds and ulcers when applied externally, and on gastric inflammation and irritation and diarrhoea when taken internally.

MAIN ACTIONS

Mullein has not been significantly investigated under clinical trial conditions, so evidence is derived from traditional, in vitro and animal studies.

Demulcent and emollient

Traditionally, these actions were thought to occur primarily within the respiratory system, especially the lungs. However, topical preparations of mullein also exert an emollient action on the skin (Blumenthal et al 2000). This is most likely due to the herb's high mucilaginous content.

Antimicrobial

Antiviral action

Mullein extract exhibits in vitro antiviral activity against fowl plague virus, several influenza A strains and influenza B strain, as well as HSV (McCutcheon et al 1995, Serkedjieva 2000, Slagowska et al 1987, Zanon et al 1999, Zgorniak-Nowosielska et al 1991). Antiviral activity has been demonstrated for both infusions and alcoholic extracts (Serkedjieva 2000).

Antibacterial action

In vitro studies have demonstrated antibacterial activity for mullein extracts (aqueous, ethanol and methanol) against *Klebsiella pneumonia*, *Staphylococcus aureus*, *Staphylococcus epidermidis* and *Escherichia coli* (Turker & Camper 2002). Of the three extracts tested, the aqueous extract exhibited the strongest antibacterial action.

Antitumour

Some plants, such as mullein, were used in folk medicine as sources of antitumour remedies. An in vitro study has identified inhibitors of protein biosynthesis in *Verbascum thapsiforme* flowers. Researchers found that a saponin glycoside and its aglycon, isolated from the flowers, directly inactivates ribosomes (Galasinski et al 1996). The constituent, verbascoside, has been shown to inhibit telomerase activity in human gastric carcinoma cells in test tube studies, resulting in inhibition of tumour growth (Zhang et al 2002). Cytotoxic effects for verbascoside have also been identified against rat hepatoma and sarcoma cells, and cytostatic activity on human epithelial carcinoma cells (Saracoglu et al 1995).

OTHER ACTIONS

The verbascoside constituent demonstrates antioxidant activity in vitro (Gao et al 1999). The saponins in mullein are thought to exert an expectorant activity; however, further investigation is required to confirm this.

CLINICAL USE

Mullein has not been subjected to significant clinical investigation; therefore, information is generally derived from traditional usage, phytochemical research or evidence of pharmacological activity. In practice, this herbal medicine is often combined with other herbs in order to strengthen clinical effects.

Chronic otitis media

To date, no controlled studies are available to determine the clinical effectiveness of mullein as a standalone treatment. However, two double-blind studies that tested a herbal combination ear-drop product (containing mullein) in children have produced positive results. The first study involved 103 children aged 6–18 years and found that a naturopathic herbal ear drop known commercially as Otikon (consisting of *Allium sativum*, *Verbascum thapsus*, *Calendula* flowers and *Hypericum perforatum* in olive oil) was as effective as local anaesthetic ear drops (containing ametocaine and phenazone in glycerin) in the management of ear pain associated with acute otitis media. Treatment lasted for 3 days and produced a statistically significant improvement (Sarrell et al 2001). The second was a randomised, double-blind study involving 171 children aged 5–18 years who had otalgia and clinical findings associated with middle-ear infection (Sarrell et al 2003). Children receiving herbal ear drops containing *Allium sativum*, *Verbascum thapsus*, *Calendula* flowers, *Hypericum perfoliatum*, lavender and vitamin E in olive oil achieved better pain relief than controls; however, the pain appeared to be self-limiting with significant improvements seen in all groups over 3 days. The dose used was 5 drops three times daily.

Productive and dry cough

Traditionally, mullein is combined with other demulcent or expectorant herbal medicines such as *Glycyrrhiza glabra*, *Tussilago farfara* and *Althaea officinalis* in the treatment of productive cough.

Commission E approves the use of mullein flowers for catarrhs of the respiratory tract (Blumenthal et al 2000). This is largely based on traditional use extending back to ancient times, and phytochemical investigation from in vitro and in vivo studies.

Topical use

Mullein is used topically for wounds, burns, bruises, haemorrhoids and pruritus, and to soften the skin. The high mucilage and tannin content of the herb provides a theoretical basis for its use in these situations as an antipruritic and astringent agent. The leaves are used topically to soften and protect the skin. To date, no controlled studies are available to determine its effectiveness.

OTHER USES

Mullein is included in herbal combination treatments for a variety of respiratory conditions such as bronchitis, asthma and tracheitis. Traditionally it is also used for diarrhoea, dysentery, haemorrhoids and laryngitis. In manufacturing, mullein is used as a flavouring component in alcoholic beverages.

DOSAGE RANGE

- Fluid extract (1:1): 1.5–2 mL twice daily.
- Tincture (1:5): 7.5–10 mL twice daily.
- Dried leaf: 12–24 g/day.
- Decoction: 1.5–2 g of herb in 250 mL of cold water, brought to the boil for 10 minutes, taken twice daily.

ADVERSE REACTIONS

A case of contact dermatitis has been reported (Romaguera et al 1985).

SIGNIFICANT INTERACTIONS

Controlled studies are not available.

CONTRAINDICATIONS AND PRECAUTIONS

Insufficient reliable information is available.

PREGNANCY USE

Insufficient reliable information is available; however, Commission E states that no restrictions are known (Blumenthal et al 2000).

PATIENTS' FAQs

What will this herb do for me?

Mullein has been used since ancient times as a treatment for productive coughs and catarrhal states. In modern times, it is also used to treat chronic otitis media, and has antiviral action against influenza virus and HSV. Currently, more scientific investigation is required to confirm efficacy for these indications.

PRACTICE POINTS/PATIENT COUNSELLING

- Mullein flowers have been used since ancient times as an expectorant and anticatarrhal agent in conditions of productive cough and respiratory infections.
- It is most commonly used in combination with other demulcent and expectorant herbal medicines in the treatment of productive and dry cough.
- In vitro studies have identified antiviral and antibacterial activity.
- Mullein has not been subjected to significant clinical investigation; therefore, information is generally derived from traditional usage or evidence of pharmacological activity. As such, Commission E approves its use for catarrhs of the respiratory tract.
- Used in the form of a herbal combination ear drop, significant anaesthetic activity has been demonstrated.

When will it start to work?

Ear drops containing mullein within a herbal combination exerted significant anaesthetic effects within 1–2 days.

Are there any safety issues?

Although safety has not been scientifically established, a long history of use suggests that it is a safe substance when used at the recommended doses.

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Myrrh

HISTORICAL NOTE The resin that seeps out of the bark of the *Commiphora* plant has been considered an important medicinal product in the Middle East, China and India since biblical times. Because of its antimicrobial activity, myrrh has historically been used, alone and in combination with other herbs, to treat infections and inflammations of the oral cavity, in purification rituals, to embalm bodies, dress infected wounds and as a treatment for leprosy.

COMMON NAME

Myrrh

OTHER NAMES

Abyssinian myrrh, bal, bol, common myrrh, heerabol, hirabol myrrh, gum myrrh tree, gummi myrrh, Somali myrrh, Yemen myrrh

BOTANICAL NAME/FAMILY

Commiphora molmol (family Burseraceae)

PLANT PARTS USED

Gum resin, stem, leaves

CHEMICAL COMPONENTS

Myrrh contains three main components: gum resin 30–60%; alcohol-soluble resins 20–40%; volatile oils (2–10%).

Guggul is the oleo-gum-resin exudate from *Commiphora mukul*, which is also used therapeutically and has been scientifically investigated.

Resins are sticky, water-insoluble substances that are secreted where a plant is damaged by incision or natural causes. The viscous substance hardens shortly after secretion, but may be returned to a liquid state with heating. Resins tend to be soluble in alcohol. Guggulipid is extracted from guggul and contains plant sterols (guggulsterones E and Z) which are thought to be its main pharmacologically active constituents (Ulbricht et al 2005).

MAIN ACTIONS

Antiseptic

Antifungal and antibacterial activities have been observed in vitro against standard pathogenic strains of *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Candida albicans* (Dolara et al 2000). The oleo-gum-resin of *C. mukul* was shown to be comparable to kanamycin against both Gram-positive and Gram-negative bacteria in vitro (Saeed & Sabir 2004).

Antiparasitic

Antiparasitic effects have been shown against *Schistosoma mansoni* in mouse livers in vitro (Hamed & Hetta 2005). Liver enzymes were significantly decreased after treatment with myrrh (*C. molmol*), whilst ova and worms' numbers were noticeably decreased. An in vivo study in the same year also produced promising results (Massoud et al 2005). Myrrh (500 mg/kg) was given for 5 days, 8 weeks postinfection. The animals were sacrificed after 12 weeks from the beginning of the experiment and myrrh was found to be comparable to cremophore EL, both producing approximate normal liver histology as compared to untreated animals. Another study compared the toxicity of myrrh to the commonly-used antischistosoma drug Praziquantel. Praziquantel is well known for its toxicity and it would be a distinct advantage if another safer product could be found. The researchers reported that myrrh is a safe and promising alternative without hepatotoxic, genotoxic and carcinogenic consequences.

Mirazid, an oleo-resin, derived from myrrh may also be effective against heterophyiasis with an animal study reporting a 100% reduction in worm load after 3 days (Fathy et al 2005).

Lipid-lowering effects

Several mechanisms of action are considered responsible for this effect. The guggulsterones act as antagonists of the bile-acid receptor and of the farsenoid X receptor, which are involved in bile-acid regulation and cholesterol metabolism. Crude guggul contains ion-exchange resins that may remove bile from the intrahepatic circulation (Urizar et al 2002, Wu et al 2002).

According to one review, 11 clinical studies have generally demonstrated that guggulipid from *C. mukul* significantly reduces triglyceride and total cholesterol levels; however, results from a recent double-blind randomised study were negative (Ulbricht et al 2005).

Anti-inflammatory

Myrrhanol A, a triterpene isolated from *C. mukul* gum resin, produces potent anti-inflammatory activity, as observed in an animal model of inflammation. In this study, anti-inflammatory activity was more marked than that of hydrocortisone (Kimura et al 2001). An animal model of rheumatoid arthritis (RA) confirmed significant anti-inflammatory effects with oral administration, also resulting in decreased joint swelling (Sharma & Sharma 1977). The essential oil of myrrh has also been shown to inhibit IL-6, probably due to down-regulating PGE2 production but not via nuclear factor kappaB inhibition in human gingival fibroblasts (Tipton et al 2006). Conversely, guggulsterone from *C. mukul* has demonstrated anti-inflammatory effects by decreasing nuclear factor kappaB and therefore tumor cell-induced osteoclastogenesis in vitro (Ichikawa & Aggarwal 2006).

Local anaesthetic

Several compounds found within myrrh exert local anaesthetic activity, chiefly by blocking the inward sodium current across membranes (Dolara et al 2000).

OTHER ACTIONS

Antispasmodic

One major component, T-cadinol, and several minor components possess smooth muscle-relaxing properties according to ex vivo tests (Andersson et al 1997, Claeson et al 1991).

Increases glucose tolerance

An extract of myrrh effectively increased glucose tolerance in both normal and diabetic rats (Al-Awadi & Gumaa 1987). Guggulipid (20 g/kg) improved glucose tolerance in another in vivo study (Cornick et al 2008). The purified ethyl ester of commipheric acid (150 mg/kg, twice daily) also lowered fasting blood glucose, insulin and triglycerides leading researchers to propose that this constituent may be at least partly responsible for the antidiabetic effects; however, oral bioavailability is poor.

Local astringent and enhanced wound healing

Myrrh has astringent activity, promotes tissue granulation and enhances wound healing (Blumenthal 2000).

CLINICAL USE

Topical treatment of oral or pharyngeal inflammation

Often used as a component of gargles, mouthwashes or paints for these indications, there are few controlled clinical trials or in vitro studies on the effects of myrrh on cells derived from the human oral cavity. A 2003 in vitro study investigating the effects of myrrh oil on a number of key cells implicated in gingivitis found that low concentrations of myrrh oil reduced gingival fibroblast production of proinflammatory cytokines and, therefore, the participation of these cells in gingival inflammation

associated with gingivitis and periodontitis (Tipton et al 2003). This is thought to be, at least in part, due to inhibition of PGE2 (Tipton et al 2005).

Commission E approved myrrh for these indications (Blumenthal 2000).

External treatment of minor inflammatory conditions and wounds

Myrrh is incorporated into salves and topical preparations for the treatment of bed sores, minor wounds and haemorrhoids. Although no clinical trials are available, the antimicrobial, anti-inflammatory, astringent and local anaesthetic activities of myrrh provide a theoretical basis for efficacy.

Osteoarthritis

A small, uncontrolled trial of *C. mukul* for patients with osteoarthritis (n = 30) demonstrated that treatment with 500 mg (3.5% guggulsterones) of the herb, three times daily for 2 months resulted in reduced joint inflammation, swelling and pain (Singh et al 2003). Although this suggests that the effects may be clinically significant, further investigation is required.

Hyperlipidaemia, hypercholesterolaemia, hypertriglyceridaemia

Various RCTs have investigated the effects of guggulipid on high-blood levels of lipids, cholesterol and triglycerides with inconsistent results. Overall, effects seem to be more likely in Indian populations than people eating Western diets; however, the reason for the discrepancy is unknown.

Szapary et al (2003) conducted a double-blind, placebo-controlled, randomised trial with 103 subjects with LDL cholesterol levels of 3.37–5.19 mmol/L. A standardised dose of 1000 mg of guggulipid (containing 2.5% guggulsterones) was given to one treatment group, while a higher standardised dose of 2000 mg was given to the other, three times daily for 8 weeks. Results showed a decrease of LDL cholesterol in the placebo group of 5%, an increase of 4% in the 1000 mg group and an increase of 5% in the 2000 mg group. Overall this constituted a 9% and a 10% increase in LDL cholesterol with guggulipid treatment. In comparison, several randomised clinical trials and in vivo tests using various extracts of guggul have reported significant lowering of total cholesterol, triglycerides and LDL cholesterol levels and increases in HDL cholesterol (Gopal et al 1986, Malhotra et al 1977, Nityanand et al 1989, Singh et al 1990). In two reports, the duration of the lipid-lowering effect continued for 6–20 weeks after discontinuation of therapy (Gopal et al 1986, Nityanand et al 1989). One clinical study showed that the lipid-lowering effects of a preparation of guggul fraction A (1.5 g/day) were similar to clofibrate (2 g/day) (Malhotra et al 1977). A larger study of 235 volunteers conducted under double-blind randomised conditions showed that patients with hypercholesterolaemia responded better to guggulipid (1.5 g/day) than to clofibrate (1.5 g/day). However, those with hypertriglyceridaemia responded better to clofibrate (Nityanand et al 1989). Many of these trials have been criticised for being small and methodologically flawed or poorly reported (Ulbricht et al 2005).

However, a more recent review stated a difference in opinion and concluded that the trials were of reasonable quality (Singh et al 2007). They found that over 80% of trials using guggul produced favorable results. Again, more large-scale clinical trials need to be done to assess the efficacy of guggulipid in hypercholesterolaemia.

OTHER USES

Traditional indications

Myrrh has been used in traditional Chinese medicine, Tibetan medicine, Ayurvedic medicine, Middle Eastern medicine and in Europe; therefore, it has numerous traditional indications. Myrrh has been used to treat infections, respiratory conditions, mouth ulcers, gingivitis, pharyngitis, respiratory catarrh, dysmenorrhoea, amenorrhoea, menopausal symptoms, wounds and haemorrhoids. It has also been used to treat arthritis and as an embalming agent.

Parasitic diseases

Schistosomiasis

Schistosomiasis is an important trematode infection affecting over 200 million people in the tropics and subtropics (Kumar & Clark 2002). After malaria, it is the next most important parasitic disease with chronic infection causing significant morbidity. Currently, the drug praziquantel is often recommended, but it does not affect the immature stage and may not abort an early infection. Additionally, a drug-resistant strain has developed (Beers & Berkow 2003). Due to these factors, there is great interest in discovering alternative treatments.

One clinical study involving 204 patients with schistosomiasis produced impressive results with a 3-day oral dose regimen producing a cure rate of 92% (Sheir et al 2001). Re-treatment of non-responders increased the overall cure rate to 98%. A field study produced similar results with 97.4% of subjects infected with the *Schistosoma haematobium* strain and 96.2% infected with the *S. mansoni* strain successfully clearing the parasite after ingesting 1200 mg of *Commiphora molmol* daily for 6 days (Abo-Madyan et al 2004a). However, two randomised trials, controlled with the drug praziquantel, have both shown little effectiveness of myrrh against the parasite (Barakat et al 2005, Botros et al 2005).

Fascioliasis

Human fascioliasis occurs in Europe, Africa, China and South America and is an infection with *Fasciola hepatica*, which is acquired by eating contaminated watercress. The flukes mature in the bile ducts and cause biliary tract obstruction and liver damage (Beers & Berkow 2003).

A small study of seven infected patients found that treatment with myrrh over 6 consecutive days produced alleviation of all symptoms and signs, and a dramatic drop in egg count, with eggs no longer detected 3 weeks after treatment (Massoud

Historical note — Myrrh and mummification
Chemical treatments were an essential part of the mummification process in ancient Egypt. Several different plant products were used in the process, one of which was oil of myrrh. Interestingly, modern-day research has discovered that the oil has molluscicidal properties against several Egyptian snail species, suggesting that it may have been a wise choice for protecting mummified remains against destruction (Allam et al 2001).

et al 2001a). Furthermore, high-eosinophil counts elevated liver enzymes and *Fasciola* antibody titres returned to normal. A field study showed that myrrh (1200 mg daily for 6 days) cleared the parasite in 94.1% of infected people at the 3-month follow-up (Abo-Madyan et al 2004b).

Mosquitocidal
The oil and oleo-resin from the plant extract of *C. molmol* exhibit larvicidal activity against *Culex pipiens* larvae (Massoud et al 2001b).

Acne
Three months' treatment with guggulipid (equivalent to 25 mg guggulsterone) was found to be as effective as tetracycline in the treatment of nodulocystic acne in a randomised clinical study of 20 patients (Thappa & Dogra 1994).

DOSAGE RANGE

Internal preparations — Commiphora molmol
- Fluid extract (1:1) (g/mL): 2 mL/day.
- Tincture (1:5): 0.5–2 mL three times daily.

Internal preparations — guggulipid
- Acne: a dose equivalent to 25 mg guggulsterone taken once to twice daily.
- Hyperlipidaemia — 500–1000 mg of standardised guggulipid administered two to three times daily.

(Guggulipid preparations are often standardised to 2.5–5% of guggulsterones.)

External preparations
- Tincture (1:5) (g/mL) in 90% ethanol can be used in different concentrations to produce different therapeutic products.
- Mouthwash or gargle: 30–60 drops tincture in a glass of warm water.
- Paint: the undiluted tincture can be applied directly to gums or mucous membranes of the mouth two to three times a day.

TOXICITY
A dose of 10 mg/kg/day was given to subjects in one study with no serious adverse effects (Sheir et al 2001).

ADVERSE REACTIONS
Restlessness, mild abdominal discomfort and gastrointestinal symptoms, such as diarrhoea and nausea, have been reported, mainly with orally administered extracts. Allergic dermatitis has also been reported for topical usage. The standardised guggulsterone (guggulipid) preparations tend to be far better tolerated.

SIGNIFICANT INTERACTIONS
Interactions are theoretical and based on in vitro and in vivo data; therefore, clinical significance is unclear and remains to be confirmed.

Diabetic medication
In vivo studies suggest myrrh may have hypoglycaemic effects and therefore would have additive effects with diabetic medications. Changes in serum glucose in patients taking these medications should therefore be monitored.

Lipid-lowering medication
Guggul may have cholesterol-lowering activity and therefore have additive effects with other lipid-lowering medications — observe patients taking this combination and monitor drug requirements. Beneficial interaction is possible.

Anticoagulant and antiplatelet medication
Guggul inhibited platelet aggregation in vitro and in a clinical study; therefore, concurrent use may theoretically increase the risk of bruising and bleeding (Bordia & Chuttani 1979). It is uncertain what implications this observation has for *C. molmol* use. Observe patients taking these combinations.

Diltiazem
Reduced efficacy possible. A clinical study confirmed that guggulipid reduces bioavailability of this medicine (Dalvi et al 1994). It is uncertain what implications this observation has for *C. molmol* use. Observe patients taking this combination.

Propranolol
Reduced efficacy possible. A clinical study confirmed that guggulipid reduces bioavailability of this medicine (Dalvi et al 1994). It is uncertain what implications this observation has for *C. molmol* use. Observe patients taking this combination.

CONTRAINDICATIONS AND PRECAUTIONS
Do not use in cases of known allergy. Suspend use of guggul preparations 1 week before major surgery.

PREGNANCY USE
Safety is unknown.

PATIENTS' FAQs
What will this herb do for me?
Traditionally, the herb has been used as a mouthwash or topical paint to relieve symptoms of mouth ulcers, sore throats and gum disease. It has also been used as a topical application for inflamed skin conditions and wounds. Scientific research confirms antiseptic, anti-inflammatory and local anaesthetic effects and significant antiparasitic effects. The preparation known as guggulipid, which comes from *Commiphora* species, may lower total cholesterol levels.

PRACTICE POINTS/PATIENT COUNSELLING

- Myrrh has been used since ancient times in a variety of forms as an antiseptic, anti-inflammatory and analgesic medicine.
- It has been used as a topical preparation to reduce inflammation and enhance wound healing — in vivo evidence suggests that the anti-inflammatory activity of one of the main constituents is stronger than hydrocortisone and local anaesthetic activity is likely.
- Preliminary evidence suggests that it may be a useful treatment in gingivitis and periodontal disease.
- The preparation known as guggulipid, which comes from *Commiphora* species, may have lipid-lowering effects according to clinical studies; however, evidence is contradictory and further research is required to confirm this.
- Myrrh is not to be used in pregnancy and may interact with a number of medications when used orally.

When will it start to work?

A mouthwash or paint should provide rapid symptom relief.

Antiparasitic activity has been reported within 3 days' use in some parasitic infestations.

The lipid-lowering effects of guggulipid have been reported within 12 weeks.

Are there any safety issues?

The herb should not be taken during pregnancy and may interact with some medications.

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New Zealand green-lipped mussel

HISTORICAL NOTE The Mytilidae are a family of bivalve molluscs that first appeared approximately 400 million years ago (Scotti et al 2001). In New Zealand, they include the green-lipped mussel, which is also known as *Perna canaliculus* and has the Maori name kuku. Also known as *Perna viridis*, the green-lipped mussel has been used to treat arthritis by the Maoris for many years.

BACKGROUND AND RELEVANT PHARMACOKINETICS

There is insufficient reliable information available.

CHEMICAL COMPONENTS

Green-lipped mussel contains minerals, mucopolysaccharides and numerous other constituents; however, the protein and lipid content is considered the most important for pharmacological activity. Virtually all of the protein content is comprised of pernin, a self-aggregating glycoprotein rich in histidine and aspartic acid (Scotti et al 2001).

A lipid-rich extract, prepared by supercritical fluid (CO_2) extraction of freeze-dried stabilised NZ green-lipped mussel, is commercially available as Lyprinol. The main lipid classes in this preparation are sterol esters, triglycerides, free fatty acids (mainly EPA and DHA), sterols and phospholipids (Sinclair et al 2000).

MAIN ACTIONS

Most investigation has been conducted with one of two commercial preparations: Seatone or Lyprinol.

Anti-inflammatory

Significant anti-inflammatory activity has been observed in both humans and animals with NZ green-lipped mussel (Halpern 2000, Miller & Ormrod 1980, Miller et al 1993). The mechanism of action is not well understood, but results from test tube and animal studies suggest inhibition of leukotriene B4 synthesis and PGE_2 production by activated macrophages and prostaglandin inhibitor actions (Miller & Wu 1984, Miller et al 1993).

OTHER ACTIONS

Not known.

CLINICAL USE

Few primary sources are available, so secondary sources have been used where necessary in order to provide a more complete description of the evidence available.

Rheumatoid arthritis and osteoarthritis

Arthritis is a significant problem in both humans and animals. In dogs, the most common form of joint disease is OA, which has been successfully treated by green-lipped mussel powder in one double-blind randomised study (Bierer & Bui 2002). Active treatment was shown significantly to improve total arthritic score, and alleviate joint pain and swelling at the end of week six compared with controls. More specifically, 83% of dogs in the active treatment group experienced a 30% or greater reduction in total arthritic scores and of these, 18% showed a 70% or greater improvement. Only 7% of controls showed a 30% or greater improvement with no dogs showing a 50% or greater improvement. The doses of green-lipped mussel powder ranged from 450 mg to 1000 mg/day, depending on body weight.

Clinical testing in humans has produced inconsistent results. One randomised clinical trial using Seatone in 35 patients with RA found no significant difference in chemical or clinical parameters compared with placebo, after 6 months' use (Larkin et al 1985). However, another study found that both freeze-dried powder and lipid extract of green-lipped mussel were effective in reducing symptoms in OA and RA (Gibson & Gibson 1998). Unfortunately, further details of this second study are not available. A more recent study, also conducted over 6 months, but this time comparing Lyprinol with placebo, found an improvement in mainly subjective measurements for OA; however, the results overall were still inconclusive (Lau et al 2004).

Asthma

Forty-six patients with asthma received either Lyprinol 2 capsules or placebo daily over 8 weeks under double-blind randomised test conditions (Emelyanov et al 2002). Active treatment resulted in a significant improvement on several parameters such as daytime wheeze, reduced concentration of exhaled H_2O_2 and an increase in morning PEF, compared with placebo.

OTHER USES

A preliminary animal study has shown Lyprinol to be of potential benefit in inflammatory bowel disease. As this study compared Lyprinol with both olive oil and fish oil, it suggests that another component, beyond the fatty acid content, is providing the therapeutic benefit (Tenikoff et al 2005).

DOSAGE RANGE
The studies of NZ green-lipped mussel have used 210 mg/day of the lipid extract or 1050–1150 mg/day of the freeze-dried powder.

TOXICITY
Insufficient reliable information is available.

ADVERSE REACTIONS
Gastrointestinal discomfort, gout, skin rashes and a case of granulomatous hepatitis have been reported (Ahern et al 1980, Brooks 1980).

SIGNIFICANT INTERACTIONS
Insufficient reliable information is available.

CONTRAINDICATIONS AND PRECAUTIONS
Contraindicated in people with allergies to shellfish—use with caution in people with hypertension, as the sodium content could theoretically raise blood pressure.

PREGNANCY USE
Insufficient reliable information is available to assess safety.

PRACTICE POINTS/PATIENT COUNSELLING
- New Zealand green-lipped mussel has been used to treat arthritis by the Maoris for many years.
- Significant anti-inflammatory activity has been observed in both animals and humans.
- Although a controlled study in dogs showed significant symptom relief for OA, clinical studies have produced inconsistent results.
- One controlled study has identified possible benefits in asthma.
- Insufficient reliable information is available to determine the safety of green-lipped mussel.

PATIENTS' FAQs
What will this supplement do for me?
Some studies have showed that NZ green-lipped mussel exerts significant anti-inflammatory activity, but it is uncertain whether it will relieve symptoms of OA. One small study suggests that it may relieve some symptoms of asthma.

When will it start to work?
Effects in asthma were seen after 8 weeks' use in one study.

Are there any safety issues?
It should not be taken by people with allergies to shellfish and should be used with caution by people with high blood pressure.

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Noni

HISTORICAL NOTE Noni has been used throughout Southeast Asia and Polynesia for more than 2000 years as a food source, a medicine and a dye. Noni fruit was traditionally used by Polynesians to combat fatigue (Ma et al 2007) and legends tell of Polynesian heroes and heroines that used noni to survive from famine (Wang et al 2002).

COMMON NAME
Noni

OTHER NAMES
Ba Ji Tian, cheese fruit, Indian mulberry, meng-kudu, nhau, nono, nonu.

BOTANICAL NAME/FAMILY
Morinda citrifolia (family Rubiaceae)

PLANT PARTS USED
Roots, stems, bark, leaves, flowers, fruit and juice.

CHEMICAL COMPONENTS
Noni contains terpenoids, alkaloids, anthraquinones (e.g. damnacanthal, morindone and rubiadin), the coumarin scopoletin, beta sitosterol, carotene, vitamin A, flavone glycosides, linoleic acid, the orange-red pigment alizarin, L-asperuloside, caproic acid,

caprylic acid, ursolic acid, octanoic acid, potassium, vitamin C, rutin (Hiramatsu et al 1993, Wang et al 2002), as well as a natural precursor for xeronine named proxeronine (Heinicke 1985, 2001). In vitro studies suggest that the antioxidant activity is due to several compounds such as coumarin derivatives (Ikeda et al 2009) and phenolic compounds (Liu et al 2007) that may contribute individually or synergistically.

Scopoletin has been suggested as a bioactive marker and a candidate for product standardisation and pharmacokinetic studies (Issell et al 2008).

MAIN ACTIONS

Noni is purported to have many different effects including analgesic, anti-inflammatory, antioxidant, anticancer, antimicrobial, immune enhancement and antihypertensive activity.

Analgesic

Noni root extract has exhibited opioid-like properties, with dose-dependent analgesic properties in mice that were reversible by naloxone, together with sedative effects at higher doses (Younos et al 1990). Analgesic activity has also been reported in controlled trials using rats and mice (Wang et al 2002).

Antioxidant/anti-inflammatory

Fruit, leaf and root extracts have all been shown to exhibit antioxidant activity (Kamiya et al 2004, Zin et al 2006) and NO scavenging activity in vitro (Jagetia & Baliga 2004), with some extracts showing comparable antioxidant activity to tocopherol (Zin et al 2002, 2006), grape seed powder and pycnogenol (Wang et al 2002). The neolignan, americanin A, has shown to be a particularly potent antioxidant in vitro (Su et al 2005).

A 1-month double-blind, randomised, placebo-controlled trial involving 68 smokers found that 50 mL of noni juice twice daily significantly reduced plasma superoxide radicals and lipid peroxides (Wang et al 2002). Noni juice has also been shown to reduce oxidative stress and liver damage in carbon-tetrachloride treated rats (Wang et al 2002, 2008a, 2008b) as well as inhibit the in vitro enzymatic activity of cyclooxygenase-1 (COX-1) (Li et al 2003) and cyclooxygenase-2 (COX-2) (Wang et al 2002). The clinical significance of these findings is yet to be determined.

Antitumour

An alcoholic precipitate of noni juice significantly prolonged the life of mice with implanted tumours (Furusawa et al 2003, Hirazumi et al 1994). It is suggested that this antitumour activity is due to immunostimulatory activity because the noni precipitate was not directly cytotoxic to tumour cells, but did activate immune cells in vitro with its activity reduced by immunosuppressant drugs (Furusawa et al 2003, Hirazumi et al 1996). Noni juice has also been observed to increase the wet weight of thymus tissue in animals (Wang et al 2002) and to protect against 7,12-dimethylbenz(*a*)anthracene (DMBA)-induced DNA adduct formation in rats (Wang & Su 2001).

Noni improved survival times in cancer-implanted mice when combined with suboptimal doses of standard chemotherapeutic agents (Hirazumi & Furusawa 1999) and this is supported by in vitro studies demonstrating synergistic effects with chemotherapeutic agents (Furusawa et al 2003, Wang et al 2002).

In vitro studies have also found that noni fruit has antiproliferative activity against SKBR3 human breast adenocarcinoma cells (Moongkarndi et al 2004), and that glycosides extracted from noni inhibit cell transformation (Liu et al 2001) and ultraviolet-B (UVB)-induced activator protein-1 activity (Sang et al 2001, 2003). The anthraquinone, damnacanthal, is reported to stimulate UV-induced apoptosis in vitro (Hiwasa et al 1999).

Antimicrobial

Constituents of noni activity against *Escherichia coli* in vitro (Duncan et al 1998) and *Mycobacterium tuberculosis* (National Library of Medicine 2001), as well as the parasite *Ascaris lumbricoides* (Raj 1975); however, the clinical significance of this is undetermined. In vitro testing found that noni juice was as effective as sodium hypochlorite in reducing the smear layer when used as an endodontic irrigant (Murray et al 2008).

Ergogenic

Animal studies in aged mice have shown that noni juice improved endurance, balance and flexibility (Ma et al 2007).

Antihypertensive

The antihypertensive effects of the root extract of noni were first investigated in the 1950s (Ho 1955) and a hot-water extract of noni root is reported to have lowered the blood pressure of an anaesthetised dog (Youngken 1958).

Antidiabetic

In experimental diabetic models, noni extract displayed antihyperglycaemic as well as antioxidant effects (Kamiya et al 2008, Mahadeva Rao & Subramanian 2008).

OTHER ACTIONS

Noni has been shown to inhibit gastric emptying in male rats via a mechanism involving stimulation of cholecystokinin (CCK) secretion and CCK1 receptor activation (Pu et al 2004) and in vitro studies demonstrate inhibition of lipoprotein lipase suggesting potential use in weight management (Pak-Dek et al 2008).

CLINICAL USE

In recent years noni juice has been touted as a 'super juice' which enhances wellbeing. Noni has been reported to be of benefit for people with arthritis, diabetes, hypertension, muscle aches and pains, menstrual difficulties, headache, heart disease, atherosclerosis, AIDS, cancers, gastric ulcers, poor digestion, depression, senility and drug addiction (Wang et al 2002). Noni has not been significantly

investigated under clinical trial conditions, so evidence for its use is derived from traditional, in vitro and animal studies.

Anticancer

There are anecdotal reports of noni being used as an adjuvant immunotherapy for cancer (Wong 2004); however, further research is required to determine its role in clinical practice.

Hearing and mental health

A small placebo-controlled pilot study involving nine hearing impaired osteopenic or osteoporotic women found that ingestion of approximately 50 mL of noni juice over 3 months resulted in improved mental health and a mild protective effect on hearing. Further studies are required to determine the clinical significance of these findings (Langford et al 2004).

OTHER USES

Noni fruit may be used as a food source.

DOSAGE RANGE

There is little human research upon which to make accurate dosage recommendations.

- Juice of 25 mL (1 oz) twice daily (Wang et al 2002).

TOXICITY

No toxic effects have been found in rats (Mancebo et al 2002) even when given doses up to 80 mL/kg (Wang et al 2002). In vivo studies suggest the possibility of reproductive toxicity in rats (Muller et al 2009) while prenatal toxicity in developing rat embryos or fetuses revealed no evidence of toxicity (West et al 2008).

Three cases of hepatotoxicity related to noni juice consumption have been reported, with one case requiring urgent liver transplantation (Millonig et al 2005, Stadlbauer et al 2005) and the others recovering spontaneously after ceasing noni consumption (Millonig et al 2005, Stadlbauer et al 2005). Further investigation is required to determine the certainty of this causal association.

ADVERSE REACTIONS

There is insufficient reliable information available about the safety of noni. Allergenicity studies using guinea pigs report no allergic responses (Wang et al 2002).

SIGNIFICANT INTERACTIONS

There is one case report of noni juice consumption causing resistance to warfarin (Carr et al 2004). Further investigation is required to determine the certainty of this causal association.

CONTRAINDICATIONS AND PRECAUTIONS

Not known.

PREGNANCY USE

Likely to be safe when consumed in dietary amounts; however, safety is not known when used in larger quantities.

PRACTICE POINTS/PATIENT COUNSELLING

- Noni has been traditionally used as food and medicine for a wide range of medical conditions.
- Noni has not been significantly investigated in clinical studies, so its use is based on traditional evidence and laboratory and animal studies.
- Although it is likely to be safe, it is prudent to avoid using noni in amounts greater than those ingested as a food during pregnancy and to monitor clotting profiles if noni is used with anticoagulant medications.

PATIENTS' FAQS

What will this herb do for me?

Noni has not been significantly investigated under clinical trial conditions, so its use is based on traditional evidence and laboratory and animal studies.

When will it start to work?

There is little published evidence to indicate its speed of action, which will depend on the clinical use.

Are there are any safety issues?

Noni is generally considered safe and can be consumed as a food; however, the safety of large intakes is unknown.

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Oats

HISTORICAL NOTE Culpeper (1652) recommended that 'a poultice made of meal of oats and some oil of bay helpeth the itch and the leprosy'. By the end of the 18th century oats was the main grain used by all levels of the population in Scotland. Students would arrive at university after the summer with a bag of oatmeal to live on during the term. The older Scottish universities still call the autumn mid-term break 'Meal Monday' because traditionally at that time the students would return home to replenish their supplies. In recent years oats has gained a reputation as a superfood due to its high nutritional content and cardiovascular benefits. It is good source of B complex vitamins, protein, fat, minerals as well as the heart healthy soluble fibre known as beta-glucan which appears to improve blood glucose and cholesterol levels (Sadiq Butt et al 2008).

OTHER NAMES

Groats, green oats, green tops, haver, oat herb, oatmeal

BOTANICAL NAME/FAMILY

Avena sativa (family Poaceae [Graminaceae])

PLANT PARTS USED

The whole flowering plant, including the oat straw and the seed (also used for porridge). Oat bran is also used in some clinical trials.

CHEMICAL COMPONENTS

Beta-glucan (soluble fibre), triterpenoid saponins (including avenacosides A and B), phenolic compounds (avenanthramides A, B, C), alkaloids (including indole alkaloid, gramine, trigonelline, avenine), sterol (avenasterol), flavonoids, starch, phytates, protein (including gluten) and coumarins.

Nutrients such as silicic acid, calcium, potassium, phosphorus, iron (39 mg/kg), manganese (8.5 mg/kg), zinc (19.2 mg/kg) (Witchl & Bisset 1991), vitamins A, B-complex, C, E and K, and amino acids.

MAIN ACTIONS

Lipid lowering

Beta-glucans increase bile acid synthesis and thus decrease serum cholesterol (Andersson et al 2002). The fibre binds to cholesterol, preventing initial absorption and enterohepatic recirculation of cholesterol, and the two are excreted together.

Clinical trials have shown that oat bran contains soluble fibres, such as beta-glucan (e.g. 75 g extruded oat bran, equivalent to 11 g beta-glucan), which nearly double the serum alpha-HC (7 alpha-hydroxy-4-cholesten-3-one) concentration within 8 hours, indicating increased bile acid synthesis and thus decreased serum cholesterol (Andersson et al 2002). Recent human studies using 75 g extruded oat bran breakfast cereal daily (containing 11.6 g native beta-glucans) have confirmed similar effects. Administration of oat bran significantly increased median excretion of bile acids by 144%, decreased cholesterol absorption by 19%, increased the sum of bile acid and cholesterol excretion by 40% and increased alpha-HC concentration (reflecting bile acid synthesis) by 57% within 24 hours of consumption (Ellegard & Andersson 2007).

Beta-glucan added to a fruit drink appears to significantly reduce both total and LDL cholesterol in human subjects without affecting fat soluble antioxidant levels (Naumann et al 2006). Triglyceride levels may also be reduced. In a randomised crossover study, 27 healthy men added oat (providing 5.7 g/day beta-glucan) or wheat (control) cereal products to their usual diets for two weeks. Peak triglyceride concentration was significantly lower in the oats group compared to controls (Maki et al 2007a).

Anti-atherogenic effects

In vitro studies suggest that the polyphenolic antioxidants known as avenanthramides, present in oats, may exert anti-inflammatory and anti-atherogenic effects (Liu et al 2004). Avenanthramides have been shown to decrease the expression of endothelial proinflammatory cytokines. This is in part due to inhibition of NF-kappaB activation via inhibiting phosphorylation of IkappaB kinase (IKK) and IkappaB, and suppressing proteasome activity (Guo et al 2008). Additionally, avenanthramide C inhibits the serum-induced proliferation of vascular smooth muscle cells and increases nitric oxide production (Nie et al 2006a, b). As chronic inflammation and proliferation of vascular smooth muscle cells are involved in the initiation and development of atherosclerosis, these mechanisms may reduce atherogenesis.

Antihypertensive effects

A reduction in blood pressure has been observed in clinical trials; however, the mechanism of action has not been fully elucidated (Pins et al 2002, Saltzman et al 2001).

Blood glucose control

Oats have been shown in clinical trials to reduce the postprandial glycaemic response (Jenkins et al 2002, Pins et al 2002, Tapola et al 2005). Whilst the mechanism of action is unclear, the ability of beta-glucans to slow stomach emptying and increase the viscosity of food in the small intestine, resulting in delayed glucose absorption, is most likely a factor (Rakel 2003). The fat content of rolled oats does not appear to be responsible for either the glycaemic or the insulinaemic response (Tuomasjukka et al 2007).

While some studies have suggested that a minimum of 4 g of beta-glucans is required to produce a significant decrease in glucose and insulin responses in healthy people (Granfeldt et al 2008), other studies suggest this dose may not exert a significant response (Biorklund et al 2008). The effect is likely to be dependent not only on the amount of beta-glucan but on the amount of extractable beta-glucan in oat products (Makelainen et al 2007), which may explain inconsistent results in clinical studies.

Antioxidant

In human trials, avenanthramides (A-C) in oats have been found to be bioavailable and increase antioxidant capacity in healthy older adults. After consumption of an avenanthramide-enriched mixture extracted from oats, plasma reduced glutathione was elevated by 21% at 15 minutes ($P \leq 0.005$) and by 14% at 10 hours ($P \leq 0.05$) (Chen et al 2007).

Antipruritic/ anti-inflammatory effects

External application of oat preparations has been shown to relieve itch (Matheson et al 2001). These effects are most likely due to the potent anti-inflammatory effects of the avenanthramide constituents (Sur et al 2008). Topical application of 1–3 ppm avenanthramides alleviated inflammation in experimental models of contact hypersensitivity, neurogenic inflammation and itch (Sur et al 2008). The high concentration of starch and beta-glucan in colloidal oatmeal (produced by finely grinding the oats and boiling it to extract the colloidal material) is responsible for the protective and water-holding functions of oats (Kurtz & Wallo 2007).

Anticarcinogenic

The beta-glucans in oats have recently demonstrated anti-cytotoxic, antimutagenic and anti-tumorogenic activity (Mantovani et al 2008), however further investigation is needed to confirm these effects.

OTHER ACTIONS

Due to its vitamin, mineral and amino acid content, oats are a nutritious food. Internally, oats also act as a bulk-forming laxative.

CLINICAL USE

Oats are not usually used as a stand-alone treatment and tend to form part of an overall management program.

Hyperlipidaemia

Several clinical trials have shown a marked reduction in total and/or LDL-cholesterol using oat-based beta-glucan containing products (Karmally et al 2005, Saltzman et al 2001, Queenan et al 2007).

Oat bran has been shown to reduce LDL-cholesterol by 16% in 140 hypercholesterolaemic subjects consuming 56 g oat bran/day for 12 weeks (Davidson et al 1991). In overweight men consuming an oat-based cereal (14 g dietary fibre) for 12 weeks, LDL-cholesterol was most significantly affected, with a reduction in concentrations of small, dense LDL-cholesterol and LDL particle number. No adverse changes occurred in blood triacylglycerol or HDL-cholesterol concentration (Davy et al 2002). In another clinical trial, a group consuming wholegrain oat-based cereals experienced a 24.2 mg/dL reduction in total cholesterol levels and a 16.2 mg/dL decrease in LDL-cholesterol levels (Pins et al 2002).

In a controlled trial 75 hypercholesterolaemic subjects were randomised to receive 6 g/day of concentrated oat beta-glucan or placebo (dextrose) for 6 weeks. Oat beta-glucan significantly reduced total cholesterol (–0.3 ± 0.1 mmol/L) and LDL-cholesterol (–0.3 ± 0.1 mmol/L), but only the reduction in LDL-cholesterol was significantly greater than in the control group. In an intestinal fermentation model the concentrated oat beta-glucan also produced higher concentrations of the short-chain fatty acid known as butyrate than guar gum and inulin, suggesting it may have benefits for colonic health (Queenan et al 2007).

A clinical trial of 38 normotensive males (mean age 59.8 years) with mild to moderate hypercholesterolaemia and a mean body mass index (BMI) of 28.3 kg/m^2 was conducted over 8 weeks. The study investigated the effects of adding high levels of monounsaturated fatty acids plus bread formulated with 6 g of beta-glucan to the American Heart Association (AHA) Step II diet plus 60 minutes walking per day. While results were impressive, it is unclear what part the beta-glucan played in isolation (Reyna-Villasmil et al 2007).

The lipid-lowering effects of a hypocaloric diet containing oats has been shown in a clinical trial to result in significantly greater decreases in total and LDL-cholesterol than a hypocaloric diet alone (Saltzman et al 2001). In addition, a RCT of moderately hypercholesterolaemic men consuming oat milk, deprived of insoluble fibre but still containing 0.5 g/100 g beta-glucan (750 mL/day) for 5 weeks, also showed a 6% reduction in total and LDL-cholesterol (Onning et al 1999). Effects on serum lipid levels in people without hypercholesterolaemia are not well supported in clinical trials (Chen et al 2006). (See Clinical note: Major lipids affecting cardiovascular disease risk, in monograph on vitamin B_3.)

A Cochrane review has suggested that 'despite the consistency of effects seen in trials of wholegrain oats, the positive findings should be interpreted cautiously. Many of the trials identified were short term, of poor quality and had insufficient power, and most were funded by companies with commercial interests in wholegrains' (Kelly et al 2007).

Hypertension

Results of RCTs suggest that consumption of oat-based cereals may reduce systolic blood pressure (SBP) and reduce or eliminate requirements for antihypertensive medications in some people (Pins et al 2002, Saltzman et al 2001).

The inclusion of wholegrain oat-based cereals was found in an RCT to decrease blood pressure in hypertensive patients and reduce requirements for antihypertensive medications. 'Seventy-three percent of participants in the oats group versus 42% in the control group were able to stop or reduce their medication by half. Treatment group participants whose medication was not reduced had substantial decreases in blood pressure' (Pins et al 2002). In another RCT, overweight subjects consuming a hypocaloric diet containing oats (45 g/4.2 MJ dietary energy/day) for 6 weeks experienced a reduction in SBP that was more significant than a hypocaloric diet alone (oats –6 ± 7 mmHg, control –1 ± 10 mmHg, $P = 0.026$). Lipid-lowering effects were also noted (Saltzman et al 2001). In another double-blind, multicentre clinical trial, 97 hypertensive patients were randomly assigned to receive a control diet or one containing oat beta-glucan for 12 weeks. Sub-group analysis revealed that only obese patients with a BMI > 31.5 kg/m^2 experienced a significant decrease in blood pressure (SBP –8.3 mmHg, DBP –3.9 mmHg) compared to controls (Maki et al 2007b). Overall, results appear to suggest greater benefits for overweight or obese individuals.

Blood sugar regulation

The ability of oats to delay glucose absorption, and therefore reduce the postprandial glycaemic response, provides a theoretical basis for their use as part of an overall treatment protocol in diabetes and hypoglycaemic conditions. An RCT of 12 patients with type 2 diabetes demonstrated that 30 g oat bran flour, high in beta-glucan, had a low glycaemic response and decreased the postprandial glycaemic response of an oral glucose load in a series of 2-hour meal glucose tolerance tests (Tapola et al 2005).

An RCT has shown that in a 50 g portion of carbohydrate, each gram of beta-glucan reduces the GI by 4 units, making it a useful adjunct to reduce the postprandial glycaemic response without affecting palatability (Jenkins et al 2002). Another trial showed a 15.03 mg/dL drop in plasma glucose levels versus controls when consuming wholegrain oat-based cereals (Pins et al 2002). Processing methods may affect the benefits of oats with a small study demonstrating that processing oat beta-glucan through enzymatic, rather than by aqueous methods, preserves the viscosity and improves postprandial glycaemic control (Panahi et al 2007).

In an uncontrolled pilot study, 14 hospitalised patients with metabolic syndrome were given a diabetes-adapted hypocaloric diet (1500 kcal/day; 50–55% carbohydrate, 15–20% protein, 30% fat) for 5 days with or without a 2-day period (third and fourth day) where the diet included 15 carbohydrate units of oatmeal (1200 kcal/day; 63% carbohydrate, 12% protein, 6% fat and 16.2 g fibre). The oatmeal intervention reduced insulin requirements by 42.5% and the effect persisted after a 4-week

outpatient period (Lammert et al 2008). The differences in calorie intake and nutritional breakdown make it difficult to attribute the observed effects to oatmeal alone and more controlled studies have been planned.

Pruritus

Oatmeal has been used traditionally to relieve the itch and irritation associated with various dry, itchy skin conditions. Colloidal oatmeal lotion has been shown to be an effective treatment for pruritus (Talsania et al 2008). These effects may be explained by the avenanthramides, potent anti-inflammatory agents that appear to mediate the anti-irritant effects of oats (Sur et al 2008). In addition, the beta-glucan and starch in colloidal oatmeal is thought to possess water-holding effects (Kurtz & Wallo 2007).

A clinical trial assessing the itch experienced by burns patients found that the group using a product with 5% colloidal oatmeal reported significantly less itch and requested significantly less antihistamine treatment than the control group (Matheson et al 2001).

Commission E approves topical use in baths for inflammatory and seborrhoeic skin disease, especially with itch (Blumenthal et al 2000).

Atopic dermatitis

In a controlled trial, an emollient treatment (containing oat extract) for 6 weeks significantly reduced high-potency topical corticosteroid consumption (–42%; $P < 0.05$) in infants with atopic dermatitis (AD). Significant effects were not demonstrated for moderate-potency corticosteroids (Grimalt et al 2007). However, it should be noted that percutaneous sensitisation to oats used in emollients and moisturisers has been reported and one study found that 32% of children with AD using oat-based creams had an oat-positive atopy patch test (APT) vs 0% of nonusers (Boussault et al 2007). Given the hyperpermeability of infant skin, topical products containing potentially allergenic food proteins should be used cautiously (Codreanu et al 2006).

OTHER USES

Traditionally, oats are considered a nervous system nutritive and therefore used during times of convalescence. More specifically, the straw is prescribed for nervous debility and exhaustion, whereas the seed is considered more stimulating and said to gently improve energy and support an overly stressed nervous system (Chevallier 1996).

Preliminary trials have suggested an improvement in sexual interest and performance in people taking oats in combination with nettles. The effects were more consistent in males than females. Further trials are required to confirm the benefits of oats in isolation (Haroian et al 1987).

Interestingly, oats are also used as supportive therapy during nicotine (Beglinger et al 1977, Schmidt & Geckeler 1976) and morphine withdrawal; however, reliable clinical evidence is currently limited and does not fully support these recommendations.

Due to its high soluble fibre content, oats are also used as an aid to weight loss. Taken before meals, they increase satiety and therefore enable smaller food portions to satisfy hunger.

DOSAGE RANGE

- 1–4 g three times daily of oatmeal or straw (Mills 1991).
- Australian manufacturers recommend 20–40 mL/week 1:2 tincture.
- Topically for itch: 5% colloidal oatmeal in a suitable carrier (Matheson et al 2001) or 100 g cut herb in a bath (Blumenthal et al 2000).
- The inclusion of wholegrain oat-based cereals or oat bran may be a useful adjunct to the treatment of hyperlipidaemia and hypertension and to delay glucose absorption — 75 g dried oatmeal (equivalent to ≈ 3 g soluble fibre daily) (Rakel 2003). Some research indicates 6 g/day of concentrated oat beta-glucan is required for lipid-lowering effects.

ADVERSE REACTIONS

Excessive intake of fibre from oats or oat bran may cause flatulence and anal irritation.

SIGNIFICANT INTERACTIONS

Controlled studies are largely unavailable; therefore, interactions are based on evidence of activity and are largely theoretical and speculative.

Antihypertensives

Additive effects are theoretically possible (Pins et al 2002); beneficial interaction is possible — observe. Patients taking oats, oat milk or oat bran should be monitored, as medication requirements may alter.

Lipid-lowering medications

Additive effects are theoretically possible — beneficial interaction is possible. Patients taking oats, oat milk or oat bran should be monitored, as medication requirements may alter. Conversely, two case reports exist of a reduced effect of lovastatin in patients taking 50–100 g oatbran daily (Richter et al 1991). As this is likely to be due to the fibre inhibiting absorption of the drug, doses should be separated by 2–3 hours.

Insulin and diabetic medications

In an uncontrolled pilot study, an oatmeal intervention reduced insulin requirements by 42.5% in hospitalised patients with metabolic syndrome; the effect persisted after a 4-week outpatient period (Lammert et al 2008). Insulin requirements should be monitored in patients taking oat beta-glucans as a change to medication dose could be required. Beneficial interaction possible under supervision.

CONTRAINDICATIONS AND PRECAUTIONS

Given the hyperpermeability of infant skin topical products containing potentially allergenic oat proteins should be used cautiously (Codreanu et al 2006). Dietary oats should not be used in cases of intestinal obstruction (Skidmore-Roth 2001).

Clinical note — Do oats interfere with nutrient absorption?
Although the high phytate content of oats would indicate a potential for reduced absorption of trace elements such as zinc, calcium and iron, one clinical trial investigating the effects of oat bran on zinc absorption found no evidence of reduced absorption (Sandstrom et al 2000).

Coeliac disease and oats consumption

In the past oats were generally contraindicated in people with coeliac disease (CD) due to their gluten content. Recent studies however have demonstrated that oats appear to be well tolerated by the majority of adults (Kemppainen et al 2007, Guttormsen et al 2008, Lundin et al 2003) and children (Holm et al 2006, Benkebil & Nydegger 2007, Hogberg et al 2004) with CD. However, some patients display a specific small intestinal T cell response to oat peptides that cannot be explained by contamination with other cereals (Ellis & Ciclitira 2008) and may experience intestinal discomfort, diarrhoea, bloating and subtotal villous atrophy (Lundin et al 2003, Peraaho et al 2004, Storsrud et al 2003b).

Food processing techniques such as kilning do not appear to either increase or decrease the antigenic potential (Kemppainen et al 2008), however some species such as the Italian variety, Astra, and the Australian variety, Mortlock, may be more reactive (Silano et al 2007).

Two recent reviews of the literature concluded that oats is well tolerated by most patients with CD (Haboubi et al 2006, Garsed & Scott 2007) but recommended the avoidance of oat products that may have been contaminated by wheat (Garsed & Scott 2007) and regular follow-up, including small bowel biopsy (Haboubi et al 2006). The Canadian Coeliac Association recommends consumption of uncontaminated oats up to 70 g (½–¾ cup)/day for adults and up to 25 g (¼ cup)/day for children (Rashid et al 2007).

PRACTICE POINTS/PATIENT COUNSELLING

- Oats are a rich source of nutrients, such as calcium, potassium, phosphorus, iron, manganese, zinc; vitamins A, B-complex, C, E and K, and amino acids. Dietary oats also contain a significant amount of soluble fibre.
- Regular intake of wholegrain oat-based beta-glucan containing cereals may have positive effects on cardiovascular disease risk factors such as hypertension, hyperlipidaemia and glucose regulation.
- Topical use of the cut herb in the bath or 5% colloidal oatmeal in a suitable carrier is used to relieve itch.
- Traditionally, oats are viewed as a nervous system nutritive and therefore used during times of convalescence.
- Patients with coeliac disease should be able to tolerate moderate amounts of oats in the diet.

PREGNANCY USE

Oral use is considered to be safe in pregnancy and lactation (NMCD 2003).

PATIENTS' FAQs

What will this herb do for me?
Oats are a concentrated nutrient source and also contain soluble fibre. They not only provide a range of vitamins and minerals, but can reduce blood pressure, cholesterol and improve blood sugar regulation.

When will it start to work?
Scientific studies have shown that oatbran and oat-based cereals containing beta glucan may reduce cholesterol levels and blood pressure within 5–6 weeks.

Are there any safety issues?
Dietary oats should be avoided in cases of intestinal obstruction.

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Olive

HISTORICAL NOTE The olive tree is among the oldest known cultivated trees in the world. Several biblical references to olive suggest its use dates back to ancient times and victors in the early Olympic Games were crowned with its leaves. Olives and its associated products have been used widely as folk medicines in countries such as Spain, Italy, France, Greece, Israel, Morocco, Tunisia, Turkey and the Mediterranean islands. Today, the olive plant is most well known for its fruit crop and oil. The Mediterranean region produces approximately 98% of the world's total olive crop (≈ 11 million tons) (Delgado-Pertinez et al 2000), although the plant is also widespread on the Arabian peninsula, the Indian subcontinent and Asia. More recently, olive plantations have been developed in Australia and research is now being undertaken to identify the best species suited to the subtropical climate.

BOTANICAL NAME/FAMILY

Olea europaea L. (family Oleaceae)

PLANT PARTS USED

Fruit and leaf

Olive oil is made from the fruit and widely used in cooking. This review will focus on olive oil and olive leaf extracts.

CHEMICAL COMPONENTS

Olive oil contains high levels of monounsaturated fatty acids (chiefly oleic acid) and is also a source of at least 30 phenolic compounds including oleuropein, hydroxytyrosol and tyrosol and also flavonoids, squalene, beta-carotene, and alpha-tocopherol (Stark & Madar 2002).

Olive leaf extract also contains a variety of phenolic compounds, most importantly oleuropein, hydroxytyrosol and tyrosol, and also rutin, luteolin, catechin and apigenin, and various nutrients such as selenium, chromium, iron, zinc, vitamin C, beta-carotene and a wide range of amino acids (Polzonetti et al 2004). Unlike the olive fruit, olive leaf does not contain significant amounts of monounsaturated fatty acids, oleic acid or squalene (Stark & Madar 2002).

It is important to note that not all olive products contain the same concentration of phenolic compounds. Olive leaf extract and extra-virgin olive oil (acidity < 1%) are considered superior sources of phenolic compounds (Owen et al 2000) with extra-virgin olive oil containing higher amounts than refined virgin olive oil (Visioli & Galli 2002). Of these, olive leaf extract is the most concentrated. According to one test, total phenol levels ranging from 6360 to 8190 mg/L were identified in olive leaf extract (samples from Olive Products Australia) compared to 200–800 mg/L for extra-virgin olive oil (unpublished data, Department of Primary Industries Laboratory, Wagga Wagga, NSW, Australia).

MAIN ACTIONS

Most of the pharmacological effects for olive oil and olive leaf extract can be attributed to their main phenolic constituents, in particular oleuropein, hydroxytyrosol and tyrosol; however, several other biologically active constituents are also present.

Antioxidant

Numerous olive phenolics have strong free radical scavenging capacity and show a synergistic behaviour when combined, as occurs naturally in the fruit and leaf (Benavente-Garcia et al 2000). According to in vitro tests, the flavonoids, rutin, catechin and luteolin exert antioxidant effects almost 2.5-fold those of vitamin C and E and are comparable to that of lycopene (Benavente-Garcia et al 2000). Some clinical trials have shown improvement in the fatty acid profile of LDL cholesterol due to olive oil's antioxidant action (Cicero et al 2008, Gimeno et al 2007).

Anti-inflammatory and antithrombotic

Several constituents within olive oil and/or leaf have demonstrated anti-inflammatory properties, chiefly oleuropein, hydroxytyrosol, oleic acid, luteolin and apigenin (de la Puerta et al 2000, Marin et al 2003).

Oleuropein and hydroxytyrosol are found in both the oil and leaf and inhibit leukotriene B4 generation, which is involved in a wide range of pro-inflammatory pathways (Petroni et al 1997). These polyphenols are able to inhibit platelet aggregation and lipoxygenases and eicosanoid production (Andrikopoulos et al 2002, Gonzalez Correa et al 2008, Manna et al 2004). A reduction in platelet aggregation was also found in a study with healthy males using an olive leaf extract (Singh et al 2008). Two clinical trials found a reduction in the inflammatory marker C-reactive protein, when participants were given an olive oil-rich diet (Estruch et al 2006) and one trial also noted a decrease in interleukin-6 (Fito et al 2008).

Olive oil also contains large amounts of oleic acid, which is an omega-9 monounsaturated fatty acid that is converted to eicosatrienoic acid, which is then converted to leukotriene A3, which is a potent inhibitor of leukotriene B4 synthesis.

Anti-atherogenic

The oleic acid component modifies the vascular response to pro-atherogenic chemicals (such as high levels of cholesterol and the advanced glycation end products of diabetes) and inhibits endothelial adhesion molecule expression, according to test tube studies (Massaro & De Caterina 2002). The anti-atherogenic effects of olive oil may also be due to inhibition of platelet aggregating factor (PAF) (Karantonis et al 2006). A later animal study confirmed that olive leaf extract exerts a suppressive effect on the inflammatory response which may contribute to its anti-atherosclerotic activity (Wang et al 2008). A clinical study of 199 volunteers at

high risk of cardiovascular found that olive oil consumption protected against carotid atherosclerosis (Buil-Cosiales et al 2008)

Antimicrobial/antiviral

Oleuropein has antimicrobial activity against a variety of viruses, bacteria, yeasts and fungi (Aziz et al 1998, Bisignano et al 1999, Furneri et al 2002, Koutsoumanis et al 1998, Ma et al 2001, Markin et al 2003, Tassou & Nychas 1995, Tassou et al 1991); however, one study suggests that hydroxytyrosol has stronger broad-spectrum effects (Bisignano et al 1999). In vitro tests reveal that virgin olive oil exerts strong bactericidal activity against eight strains of *Helicobacter pylori* including several antibiotic resistant strains. Considering the phenols in virgin olive oil are stable in stomach acid, this may prove to have clinical benefits; however, further research will be needed to confirm the findings (Romero et al 2007). Another in vitro study found that olive leaf was active against some drug-resistant tuberculosis strains (Camacho-Corona Mdel et al 2008). Olive leaf extract also exhibited anti-HIV activity by blocking virus entry to the cells. Oleuropein and hydroxytyrosol are thought to be the principal components responsible for the activity (Lee-Huang et al 2007).

Antihypertensive

Studies have identified the Mediterranean diet, as an entity, and olive oil in particular, as significantly reducing arterial blood pressure in humans (Acin et al 2007, Ferrara et al 2000, Fito et al 2005, Perona et al 2004, 2006, Psaltopoulou et al 2004).

The hypotensive effect of olive leaves has also been well documented in vivo (Cherif et al 1996, Fehri et al 1994, Khayyal et al 2002, Somova et al 2003). One of the most recent studies tested a specially prepared olive leaf extract (EFLA943) and confirmed dose-dependent hypotensive activity when given orally to animals (Khayyal et al 2002). The precise mechanism of action responsible for the antihypertensive effect is unknown; however, it is suspected that improved endothelial function and/or calcium channel antagonist activity may be responsible (Gilani et al 2005).

Lipid lowering

Lipid lowering activity has been reported in some studies but is not consistent. It appears the phenolic content of olive products tested may influence results.

A randomised, crossover, controlled trial with 200 healthy male volunteers compared 25 mL/day of three varieties of olive oil and found all olive oils increased HDL cholesterol, decreased total cholesterol–HDL cholesterol ratio, decreased triglyceride levels and oxidative stress markers within 3 weeks. The greatest effects were seen for the oil with the highest polyphenolic content (Covas et al 2006). Similarly, a study of 772 people at high risk of cardiovascular disease found that an olive oil-rich diet given in the short term (3 months) reduced the cholesterol HDL ratio by 0.38 as compared to a low fat diet (Estruch et al 2006). In contrast, a dose of 50 mL/day of refined olive oil or virgin olive oil failed to significantly alter lipid profiles after 6 weeks of treatment according to a small placebo-controlled, crossover, randomised trial (Fito et al 2008). It seems that further quality clinical studies are warranted to confirm a lipid lowering effect of olive oil.

Investigation with olive leaf extracts is in its infancy to date; however, there is one open study using olive leaf extract (EFLA943) which demonstrated a reduction in cholesterol levels with treatment (Perrinjaquet-Moccetti et al 2008).

Cardioprotective

It is likely that olive oil's cardioprotective effect is multifaceted. Not only does it reduce lipid oxidation and reduce LDL cholesterol, it also reduces oxidative damage, inflammation, blood pressure, has vascular benefits and is anti-atherogenic and antithrombotic (Covas 2007). In human studies, olive oil has been shown to reduce inflammatory markers and increase antioxidant status after a meal reinforcing its cardioprotective role (Bogani et al 2007, Covas et al 2006). Extra-virgin olive oil was found to inhibit NF-(kappa)B in human monocyte/macrophages in healthy volunteers. This anti-inflammatory action is thought to assist in olive oil's cardioprotective action (Brunelleschi et al 2007).

Anticarcinogenic

Close adherence to the Mediterranean diet has been associated with a reduced risk of cancer (Mitrou et al 2007). This has prompted researchers to investigate key components of the diet, such as olive oil and its major constituents, for anticarcinogenic activity (Hamdi & Castellon 2005).

Several in vitro and in vivo studies have investigated how oleuropein and other constituents of olive exert antioxidant, antimetastatic, antimutagenic and anti-angiogenic effects (Hashim et al 2008). According to one in vitro study, oleuropein inhibits the proliferation, invasiveness and migration of advanced tumour cells (Hamdi & Castellon 2005). The maslinic and oleanolic acids in an olive fruit extract inhibited cell proliferation in vitro and encouraged apoptosis without cytotoxicity in colon-cancer cells (Juan et al 2006) Other in vitro studies have confirmed that olive oil phenols inhibit the growth of colon-cancer cells and cause apoptotic death in cancer cells (Gill et al 2005, Reyes-Zurita et al in press) and oleic acid may down-regulate the over-expression of an oncogene in some breast carcinomas causing apoptotic cell death (Menendez et al 2005). Luteolin also demonstrates antimutagenic and antitumorigenic properties in vitro (Kim et al 2003).

In vivo research with olive oil at the equivalent of normal dietary levels protected against DNA oxidative damage indicating a free radical scavenging mechanism may also be involved (Fabiani et al 2008). In vitro tests with olive leaf extract were shown to inhibit the growth of human leukaemia HL-60 cells in vitro (Abaza et al 2007, Fabiani et al 2006).

Hypoglycaemic activity

Olive leaf extract has demonstrated hypoglycaemic activity in animal models and one of the compounds responsible for this activity is oleuropeoside, which produced antidiabetic activity in animals with alloxan-induced diabetes (Gonzalez et al 1992, Manna et al 2004). Oleanolic acid is another constituent found to have antidiabetic effects in a mice model (Sato et al 2007). Conflicting results from clinical trials show one recent study suggesting that dietary olive oil reduces plasma glucose levels (Estruch et al 2006) and another small study in a group of stable coronary heart disease patients noted no change in glucose levels (Fito et al 2008).

Some researchers have suggested potentiation of glucose-induced insulin release and increased peripheral uptake of glucose as the most likely mechanism of action.

OTHER ACTIONS

Traditional texts describe the leaves as astringent and antiseptic and useful when boiled in water to create a decoction for the treatment of obstinate fevers. The oil is described as a nourishing demulcent with laxative properties. Oleuropein is the phenolic constituent responsible for the typically bitter and pungent aroma associated with olives, olive oil and leaf (Manna et al 2004).

Hypo-uricaemia

In vivo tests report that olive leaf extract has a hypouricaemic effect in treated animals (Serra-Majem et al 2003).

Homocysteine lowering

A trial with rheumatoid arthritis patients found a statistically significant reduction in homocysteine levels over an 8-week period with a freeze-dried olive vegetation water (Bitler et al 2007).

CLINICAL USE

Olive oil has been studied as a stand-alone entity in some studies; however, it is generally studied as part of the Mediterranean diet where it is the principal source of fat and considered a key contributor to the diet's many healthy benefits (Serra-Majem et al 2003). As a reflection of this, research into the Mediterranean diet is included in this monograph; however, the contribution of olive oil to these results remains unclear. In contrast, olive leaf extract has not been significantly tested under clinically controlled conditions, so evidence is mainly derived from traditional, in vitro and animal studies.

Cardiovascular disease

Prevention

It has been speculated that consumption of olive oil reduces the incidence of coronary heart disease, based on the observation that countries where the Mediterranean diet is consumed, chiefly Greece, Italy and Spain, have a lower incidence of coronary heart disease.

In 1999, the Lyon Diet Heart Study was published and is widely claimed to be a landmark study investigating whether a Mediterranean-type diet could reduce the rate of myocardial infarction (de Lorgeril et al 1999). It was a randomised secondary prevention trial that used a Mediterranean-type diet (with butter and cream replaced by a margarine based on rapeseed/canola oil and rich in alpha-linolenic acid). At a mean follow-up of 27 months, there was a 73% decrease in combined end points of cardiac death and non-fatal myocardial infarction, with a 70% decrease in cardiac death in the group eating the Mediterranean-style diet. Benefits were maintained for nearly 4 years after follow-up, which translates to 12 lives saved per 300 people in 27 months. Interestingly, these impressive results were obtained without lowering blood pressure, LDL cholesterol and triglycerides, or raising HDL cholesterol.

> ***Clinical note — What is the Mediterranean diet?***
> The Mediterranean diet studied in most trials is based on the traditional diet of Greece. It is low in saturated fat and high in monounsaturated fat (oleic acid:omega-9 = 18:1), mainly from olive oil; high in complex carbohydrates, from legumes; and high in fibre, mostly from vegetables and fruits. Total fat may be high (> 40% of total energy intake), but the monounsaturated to saturated fat ratio is around 2. The high content of vegetables, fresh fruits, cereals, and olive oil guarantees a high intake of beta-carotene, vitamins B_6, B_{12}, C and E, polyphenols and various minerals.

Several years later, data from the CARDIO2000 multicentre study was used to investigate the association between acute coronary syndromes (ACS) and a Mediterranean-style diet. Once again it was shown that the Mediterranean diet reduced the risk of developing ACS regardless of the presence of other risk factors such as hyperlipidaemia, type 2 diabetes or a sedentary lifestyle (Panagiotakos et al 2002). In this instance, primary prevention benefits were observed.

Positive results were also seen with the Indo-Mediterranean diet, which has increased intakes of whole grains, walnuts and almonds, fruit and vegetables (Singh et al 2002). The randomised trial involving 1000 patients with angina pectoris, myocardial infarction or other risk factors for coronary artery disease compared the Indo-Mediterranean diet to the Step I National Cholesterol Education Program diet and found that total cardiac end points were significantly fewer with the Indo-Mediterranean diet, as were sudden cardiac deaths and non-fatal myocardial infarctions.

Recently, a number of large, long-term studies have confirmed these findings. One epidemiological study evaluated the dietary habits of 2101 Greek men and women with no cardiovascular symptoms at baseline over 5 years. The study found that daily fruit, vegetable and olive oil intake was associated with a reduced cardiovascular risk (Panagiotakos et al 2009). A very large prospective study completed by the National Institutes of Health (NIH) in the United States showed that the Mediterranean diet

was associated with reduced all-cause and cause-specific mortality including deaths due to both cancer and cardiovascular disease (CVD) (Mitrou et al 2007). This study involved 214,284 men and 166,012 women. Another study following 40,000 migrants to Australia from Mediterranean countries revealed that the traditional Mediterranean diet was associated with reduced cardiovascular mortality (Harriss et al 2007). The Mediterranean diet can also have benefits for people with established cardiovascular disease according to a population study of 1302 patients. Those that adhered to the diet experienced a significant 27% lower mortality rate (Trichopoulou et al 2005).

Overall, these results suggest that the Mediterranean diet has both primary and secondary prevention effects.

There are also recent studies supporting the various cardioprotective actions of olive oil including a randomised, placebo-controlled study with 848 patients who had experienced a first event of acute coronary syndrome. The findings from food frequency questionnaires revealed that exclusive use of olive oil in cooking was associated with a 47% lower likelihood of having an acute coronary syndrome. This protection against coronary heart disease was not discovered with the use of other oils and fats or a combination of olive oil and other oils and fats (Kontogianni et al 2007).

Virgin versus refined olive oil?

The concentration of phenolic compounds found in olive oil varies widely depending on whether the oil is common, refined, virgin or extra virgin. It may also be affected by storage conditions, method of production and growing conditions. The main phenolic compounds, hydroxytyrosol, tyrosol and oleuropein, are highest in extra-virgin olive oil. Researchers are now comparing the different oils for their clinical effects and studies are finding that extra-virgin olive oil results in a greater antioxidant effect on lipid oxidation. It seems that a daily dose of approximately 25 mL of virgin or extra-virgin olive oil may reduce oxidative damage to LDL cholesterol (Gimeno et al 2007).

Hypertension

Both olive oil and olive leaf extract have demonstrated blood pressure lowering ability in small intervention trials, and long-term dietary intake of olive oil is associated with reduced incidence of hypertension.

Olive oil

One randomised, double-blind, crossover study compared the effects of monounsaturated fatty acid (MUFA) (extra-virgin olive oil) and polyunsaturated fatty acid (PUFA) (sunflower oil) in 23 hypertensive patients over 6 months (Ferrara et al 2000). MUFA intake resulted in significantly reduced resting blood pressure compared to the PUFA diet, but most impressively, daily drug dosage was significantly reduced with the MUFA diet (−48% vs −4%, $P < 0.005$).

A randomised, placebo-controlled, crossover study of 40 subjects with stable coronary heart disease compared the antioxidant and antihypertensive effects of two different olive oil supplements with different phenolic compound levels (refined: 14.7 mg/kg vs virgin: 161.0 mg/kg) (Fito et al 2005). Treatment with virgin olive oil rich in phenolic compounds resulted in significantly lower plasma oxidised LDL and lipid peroxide levels, together with higher activities of glutathione peroxidase. Additionally, systolic blood pressure (SBP) was significantly decreased in the hypertensive patients; however, no changes in diastolic blood pressure (DBP) were observed.

Another randomised study involving elderly patients found that increased dietary intake of virgin olive oil significantly reduced total and LDL cholesterol in normotensive but not hypertensive volunteers, whereas virgin olive oil consumption normalised SBP in this group (136 ± 10 mmHg) compared to treatment with sunflower oil (150 ± 8 mmHg) (Perona et al 2004).

In 2004, results from two large observational studies were published which further suggested that olive oil intake has significant effects on blood pressure.

One study involved assessing data from the Greek arm of the European Prospective Investigation into Cancer and Nutrition study, which included 20,343 participants (Psaltopoulou et al 2004). Intakes of olive oil, vegetables and fruit were significantly inversely associated with both SBP and DBP, whereas cereals, meat and meat products and ethanol intake were positively associated with arterial blood pressure. Mutual adjustment between olive oil and vegetables indicated that olive oil has the dominant beneficial effect on arterial blood pressure in this population.

Another study investigated whether dietary olive oil consumption over time affected the incidence of hypertension (Alonso & Martinez-Gonzalez 2004). Data from 6863 participants with at least 2-year follow-up was used and the study found that olive oil consumption was associated with a reduced risk of hypertension among men; no association was observed among women. The researchers suggested this might be attributed to the overall lower incidence of hypertension among females and the resulting lower statistical power. A recent study, of 772 participants, using the Mediterranean diet confirmed that dietary olive oil reduced SBP by 5.9 mmHg (Estruch et al 2006).

Olive leaf

A study of olive leaf extract involving 30 subjects with essential hypertension was conducted by the Service de Cardiologie, Hospital Militaire in Tunis (Cherif et al 1996). Olive leaf extract (1600 mg/day) was administered for 3 months, after 15 days treatment with a placebo. Active treatment resulted in a statistically significant decrease in blood pressure ($P < 0.001$) in all patients and was considered well tolerated. Other interesting observations were that patients previously treated with beta-blockers noted a disappearance

of gastric symptoms during treatment with olive leaf extract. Another olive leaf extract (EFLA943) in an open study, with 40 borderline hypertensive twins, showed that treatment with 1000 mg/d of this supplement significantly decreased blood pressure and lowered cholesterol levels (Perrinjaquet-Moccetti et al 2008).

Inflammatory conditions

Olive leaf extract is used to promote symptomatic relief in various inflammatory conditions, such as osteoarthritis and asthma, and as a gargle in tonsillitis and pharyngitis. The anti-inflammatory effects demonstrated by several major components in olive leaf provide a theoretical basis for its use; however, clinical trials are not yet available to determine whether effects are significant and efficacy remains speculative.

Alternately, olive oil supplementation has been tested in some clinical studies.

Rheumatoid arthritis

In some studies of RA in which fish oil supplements have been investigated, olive oil has been used as a placebo because it was generally regarded as containing neutral fatty acids; however, in some instances olive oil produced significant improvements in disease activity, prompting further research.

Supplementation for 12 weeks with olive oil resulted in a significant decrease in pain intensity, duration of morning stiffness, time taken to walk 18 m, and fibrinogen levels and improved trends in erythrocyte sedimentation rate, C3, and right grip strength according to an early study (Darlington & Ramsey 1987). A later double-blind study found subjective measures of mean duration of morning stiffness and analogue pain score improved to the same extent as treatment with fish oil supplements after 12 weeks (Cleland et al 1988).

A 24-week double-blind, randomised study of two different dosages of fish oil (3 g/day and 6 g/day) and a single dosage of olive oil (6.8 g/day of oleic acid) was conducted with 49 subjects with active RA (Kremer et al 1990). The fish oil treatment produced better results overall; however, improvement in patients' global assessment was only observed with olive oil supplementation.

Another double-blind study of 90 patients comparing treatment with fish oils (2.6 g/day), or fish oils and olive oil (1.3 g/day and 3 g/day, respectively) or olive oil (6 g/day) over 12 months found a significant decrease in Ritchie's articular index of pain and the number of painful joints after 12 months of olive oil and also after the combined use of fish oil (1.3 g/day) and olive oil (3 g/day) (Geusens et al 1994).

More recently, a study of 43 patients investigated the effects of placebo (soy oil), fish oil (3 g/day), and a combination of fish oil (3 g/day) and 9.6 mL/day of olive oil as an adjunct to standard treatment (Berbert et al 2005). The groups receiving fish oil and the fish oil/olive oil combination experienced a statistically significant improvement in joint pain intensity, hand grip strength, duration of morning stiffness and onset of fatigue compared with placebo. Parameters that responded after 24 weeks were Ritchie's articular index for joint pains, the ability to bend down to pick up clothing from the floor and getting in and out of a car. The group using the fish oil/olive oil combination also experienced improved ability to turn taps on and off and decreased rheumatoid factor after 24 weeks. When groups were compared, the combination treatment was found to be superior, showing a significant improvement in patient global assessment after 12 weeks.

A recent randomised, double-blind, placebo-controlled trial of 90 subjects with RA or osteoarthritis found that treatment for 8 weeks with an olive extract (freeze-dried olive vegetation water at a dose of 400 mg/day) significantly reduced pain and daily living improvements compared with a placebo (Bitler et al 2007).

Cancer prevention

It has been speculated that consumption of olive oil, chiefly as an ingredient of the Mediterranean diet, may reduce the incidence of some cancers, based on the observation that the incidence of cancer overall in Mediterranean countries is lower than in Scandinavian countries, the United Kingdom and the United States (Trichopoulou et al 2000, Visioli et al 2004).

One review calculated that up to 25% of the incidence of colorectal cancer, approximately 15% of the incidence of breast cancer and approximately 10% of the incidence of prostate, pancreas and endometrial cancers could be prevented if the populations of highly developed Western countries shifted to the traditional healthy Mediterranean diet (Trichopoulou et al 2000). Although these figures are only estimates, data from observational studies is now considered strong enough to suggest that the traditional Mediterranean diet should be actively promoted in order to reduce the incidence of cancer (Visioli et al 2004). This finding was confirmed with the National Institutes of Health (NIH) prospective US study which found that the Mediterranean diet was associated with reduced deaths due to both cancer and CVD (Mitrou et al 2007).

Olive oil was shown to be significantly protective of breast cancer in a population-based study in the Spanish Canary Islands with a total of 755 women who completed a food frequency questionnaire (García-Segovia 2006). Another study looked at the influence of the Mediterranean diet on high mammographic breast density (associated with an increased risk of breast cancer). This longitudinal study assessed dietary and lifestyle information from 2000 women and found that breast density was inversely associated with olive oil consumption and was therefore a possible protective factor against breast cancer in this community (Masala et al 2006).

Diabetes

There is anecdotal evidence that people with type 2 diabetes are using olive leaf extract as an adjunct to dietary modification. One report from Morocco found that 80% of people surveyed used herbal medicines for diabetes, hypertension and cardiac disease,

and olive leaf was one of the most popular treatments (Eddouks et al 2002). A recent animal study with olive leaf extract in streptozotocin-induced diabetic rats discovered a significant reduction in various markers including a decrease in serum glucose, triglycerides and total cholesterol. Compared with the diabetic drug glibenclamide, the olive leaf was more effective (Eidi et al 2008). The significant hypoglycaemic activity reported in animal models provides a theoretical basis for its use; however, clinical testing is not yet available to determine whether effects are significant and efficacy remains speculative.

Longevity

In 2002, Panagiotakos et al found that adherence to a Mediterranean diet and healthy lifestyle (non-smoking, physically active and moderate drinking) is associated with a greater than 50% lower rate of all-cause and cause-specific mortality, such as from coronary heart disease, cardiovascular diseases and cancer (Knoops et al 2004). The cohort study involved 1507 apparently healthy men and 832 women, aged 70–90 years in 11 European countries and was conducted from 1988 until 2000.

A year later, Trichopoulou et al (2003) also reported a positive association between longevity and the Mediterranean diet, with their study showing that the benefits are significant in people aged 55 years and older.

More recently, a 2004 review of five cohort studies further confirmed these findings and concluded that there is now sufficient evidence to show that diet does indeed influence longevity and that the optimal diet for the prevention of both coronary heart disease and cancer is likely to extensively overlap with the traditional Mediterranean diet (Trichopoulou & Critselis 2004). Although it is uncertain which specific components in the Mediterranean diet are most important for its protective health benefits, olive oil, fish, plant foods and moderate wine consumption are likely candidates.

Antibacterial, antifungal and antiviral

Based on evidence of its broad-spectrum antimicrobial activity, olive leaf extract is used for the treatment of common bacterial infections such as bronchitis and tonsillitis, common fungal infections such as vaginal candidiasis, *Tinea pedis* and *Tinea capitis*, and viral infections such as herpes simplex. The in vitro antifungal activity of olive and olive oil may be useful in the topical treatment of fungal infections (Battinelli et al 2006). Currently, controlled studies are not available to determine whether treatment is effective.

OTHER USES

Olive oil is an emollient and used externally to relieve pruritis and inflamed surfaces and is used to soften and remove dry scales in eczema and psoriasis. Topically oleuropein may have potential to protect and to repair after UV damage (Perugini et al 2008). Taken internally, it is used as a laxative to soften impacted faeces. As a folk remedy, the plant is used as a diuretic, hypotensive, emollient, febrifuge and tonic, for urinary and bladder infections and for headaches (Somova et al 2003). Olive leaf extract is also used as a general tonic to improve energy and provide a sense of wellbeing.

DOSAGE RANGE

General recommendations

- Olive leaf extract (according to manufacturer's recommendations): 5 mL three times daily diluted with water or juice if necessary (Olive Leaf Australia 2006).
- Olive oil: should replace dietary intake of saturated fats and be consumed as part of a Mediterranean-style diet.

According to clinical studies

- Hypertension: 1600 mg/d of olive leaf extract or 50 mL/day of virgin olive oil.
- Rheumatoid arthritis: 6–10 g/day of olive oil long term.
- Breast cancer: highest protective effects at 30.5 g/day.
- Cardiovascular protection: 25 m–50 mL/day of virgin olive oil.

ADVERSE REACTIONS

Allergenic pollen is produced by the Oleaceae family, including the olive tree, which causes seasonal respiratory allergies in Mediterranean countries.

SIGNIFICANT INTERACTIONS

Controlled studies are not available, so interactions are theoretical and based on evidence of pharmacological activity with uncertain clinical significance.

Hypoglycaemic agents

Theoretically, an additive hypoglycaemic effect is possible but is speculative — possible beneficial interaction under professional supervision.

Hypertensive agents

Theoretically, an additive hypotensive effect is possible but is speculative — possible beneficial interaction under professional supervision.

CONTRAINDICATIONS AND PRECAUTIONS

People with known allergies to the Oleaceae family of plants should avoid this herb.

PREGNANCY USE

Olive oil is likely to be safe when consumed in dietary amounts; however, the safety of olive leaf extract is not known.

PATIENTS' FAQs

What will this herb do for me?

Long-term consumption of olive oil as part of a Mediterranean diet is likely to reduce the incidence of heart disease and promote longevity. It may also reduce the risk of cancer; however, this is less well established. Used as a stand-alone supplement, it may reduce blood pressure and improve symptoms in rheumatoid arthritis. Olive leaf extract may also be useful in hypertension and inflammatory conditions; however, little research has been conducted to confirm effectiveness.

PRACTICE POINTS/PATIENT COUNSELLING

- Consumption of olive oil has beneficial effects on arterial blood pressure and reduces the risk of cardiovascular disease when ingested as part of the Mediterranean diet.
- Several studies have demonstrated that supplemental olive oil produces significant improvements in disease activity in rheumatoid arthritis.
- When used as part of the Mediterranean diet, olive oil may reduce the incidence of some cancers and increase longevity.
- Olive leaf extract contains a greater concentration of biologically active phenolic compounds than olive oil; however, it has not been significantly studied in clinical trials.
- Preliminary studies with olive leaf extract show that it has significant anti-inflammatory and antioxidant activity and possibly hypoglycaemic effects.

When will it start to work?

In rheumatoid arthritis, benefits start to appear after 12 weeks with further improvement noticed after 24 weeks. In regards to other health benefits, olive oil should be used long term.

Are there any safety issues?

Dietary amounts of olive oil are well tolerated and considered safe in healthy individuals; however, the safety of olive leaf extract has not been well studied and it should be avoided in pregnancy until safety is established.

Extra-virgin olive oil is likely to have the greatest antioxidant effects.

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Orange

HISTORICAL NOTE The root word for orange is the Arabic, *narandj* (Sellar 1992). The orange is a symbol of innocence and fertility. Some scholars believe the 'golden apple' Paris presented to Venus was actually an orange. In return, Venus bestowed Helen on Paris as a reward for selecting her in a beauty contest, which eventually caused the Trojan War. The tree is indigenous to eastern Africa, Arabia and Syria and it is believed that the crusaders may have introduced the orange to Europe when they returned from the crusades. Unripe dried fruits and the fruit peel are incorporated into various products, including foods such as marmalade, alcoholic beverages such as Curaçao and medicinal products including weight loss products. The essential oil is used in perfumes, cosmetics and aromatherapy (Leung & Foster 1996), as food flavouring and to disguise the unpleasant taste of medicines. Orange blossom water has been used for centuries in Mediterranean countries to flavour cakes and beverages (Jeannot et al 2005). Orange oil is used in various alcoholic beverages such as Grand Marnier, Curaçao, Triple Sec and Chinotto (*Citrus aurantium myrtifolia*) and in Chinese medicine (*Citrus aurantium daidai*).

COMMON NAME
Orange

OTHER NAMES
Bitter orange, *Citrus sinensis*, green orange, Seville orange, Zhi Shi

BOTANICIAL NAME/FAMILY
Citrus aurantium var. *dulcis* (sweet orange) and *Citrus aurantium* var. *amara* (bitter orange or neroli) (family Rutaceae).

PLANT PARTS USED
Fruit, dried outer peel of the ripe fruit, and essential oils and floral water (orange blossom water).

CHEMICAL COMPONENTS

Bitter orange peel
Essential oil (0.2–0.5%), monoterpenes linalyl acetate, pinene, limonene, linalool, nerol, geraniol, bitter substances, flavonoids and methyl anthranilate, the alkaloid synephrine and *N*-methyltyramine (Blumenthal et al 2000, Pellati et al 2002). Synephrine is structurally similar to adrenaline.

Essential oils

Essential oil species	Major components	Minor components
Citrus aurantium var. *dulcis*	Limonene 89%	Linalool
	Myrcene 1.7%	Neral
	Beta-bisabolene 1.29%	Geranial, neral, citronellal, sabinene, myracene
Citrus aurantium var. *amara*	*d*-limonene 89–96%	Nerol, geraniol, linalyl acetate
		Bergaptene 0.069–0.073%
		Furanocoumarins (in cold pressed but not in steam distilled oils)

(From Price and Price 1995, Sellar 1992, Verzera et al 2004.)

Clinical note — Three different essential oils

C. aurantium var. *dulcis* (sweet orange) and *C. aurantium* var. *amara* (bitter orange or neroli) are obtained from the peel and are usually expressed oils.

Neroli essential oil is obtained from the flowers of *C. aurantium* var. *amara* by steam distillation and very occasionally enfleurage and is known as Neroli Bigarade, which is said to be the best Neroli essential oil available. Neroli essential oil obtained from *C. aurantium* var. *dulcis* is known as Neroli of Portugal.

Petitgrain is obtained from the leaves of *C. aurantium* var. *amara* by steam distillation.

Each of these oils has a different chemical profile and, therefore, different uses. Distilled essential oils are used more in food flavourings and expressed essential oils in aromatherapy and perfumes because of their stronger fragrance (Tisserand & Balacs 1995). This monograph concentrates on expressed sweet orange and bitter orange essential oils.

Terpeneless/deterpenated or concentrated orange oil is sometimes available. Although the terpenes are removed, terpeneless orange oils retain all their other chemical components, including the furanocoumarins, which are in larger amounts, and this increases their phototoxic potential. Therefore, the safe concentration in blends containing terpeneless oils is less than 0.2% (Tisserand & Balacs 1995).

Methyl anthranilate is an important compound that may give orange flowers their aroma (Jeannot et al 2005).

The composition of orange essential oils is described by the International Standards Organisation (ISO) under the following standard numbers 1340: 2005:

9844: 1991	Bitter orange *C. aurantium* var. *amara*
8901: 2003	*C. aurantium* (petitgrain)
3517: 2002	*C. aurantium* var. *amara* (neroli)
4735: 2002	Oils of citrus

MAIN ACTIONS

Sympathomimetic

Considering *C. aurantium* contains biologically active adrenergic amines, it may exert sympathomimetic activity.

An in vivo study found no significant effects on blood pressure when two concentrations of *C. aurantum* tincture (standardised to 4% synephrine or 6% synephrine) were administered (Calapai et al 1999). However, analysis of myocardial electrical activity showed ECG alterations such as ventricular arrhythmias with enlarged QRS complex. The effect was present after 5 days of treatment and became significant at day 10 and was still evident after 15 days. These effects may be explained by the positive chronotropic activity of synephrine, which has been observed on isolated atria from reserpinised guinea pigs due to beta$_1$-adrenoceptor agonist activity, but could also be due to other constituents.

Appetite suppressant

Synephrine produces effects on human metabolism, which could be useful for reducing fat mass in obese humans because it stimulates lipolysis, raises metabolic rate and fat oxidation through increased thermogenesis (Pellati et al 2002). A controlled in vivo study of *C. aurantium* fruit hydro-alcoholic extracts standardised to synephrine 4% (Ci. au. 4%) and 6% (Ci. au. 6%) found that repeated administration of the extract significantly and dose-dependently reduced food intake and body weight gain (Calapai et al 1999).

Antibacterial

Seville orange has strong in vitro antibacterial activity against *Escherichia coli* and *Staphylococcus aureus* (Melendez & Capriles 2006).

Antiviral

The fruit of *C. aurantium* has a potent inhibitory activity on rotavirus infection (Kim et al 2000). The active components are neohesperidin and hesperidin.

Antifungal

Bitter orange essential oil has been shown to be effective in treating resistant fungal skin conditions (Ramadan et al 1996).

Digestive effects

The essential oil of *C. aurantium* var. *dulcis* is believed to aid digestion by stimulating the flow of gastric juice and has antispasmodic and carminative actions. The essential oil of *C. aurantium* var. *amara* is considered to be a liver stimulant, reduces gastric spasm and relieves symptoms of indigestion (Price & Price 1995, Wichtl & Bisset 1994). It is also thought to lower cholesterol.

Aromatherapy effects

The essential oil of *C. aurantium* var. *dulcis* is considered to convey warmth and happiness and improve mood (Battaglia 1997), reduce stress, aid sleep by reducing stress (Miyake et al 1991), and aid concentration. The essential oil of *Citrus aurantium* var. *amara* is considered to have a calming effect and is considered one of the most effective sedative essential oils (Battaglia 1997, Price & Price 1995, Wichtl & Bisset 1994).

OTHER ACTIONS

Antioxidant

Natural antioxidants obtained from 'citrus oils' have been shown to inhibit oxidation of LDL cholesterol in in vitro studies (Takahashi et al 2003), possibly due to the gamma-terpinene content. Terpinolene and alpha-terpinene also showed antioxidant properties. Takahashi et al suggested gamma-terpinene could be added to foods and beverages to prevent oxidation. Sellar (1992) suggested that sweet orange oil aids the absorption of vitamin C.

CYP3A4 inhibition

Bergamottin and 6′,7′-dihydroxybergamottin found in Seville oranges inactivate intestinal CYP3A4, as demonstrated clinically. Other furanocoumarins, including bergapten, could also be involved (Malhotra et al 2001).

CLINICAL USE

Heartburn and dyspeptic symptoms

The primary indication for bitter orange tincture or extract is heartburn (Blumenthal et al 2000). The dried peel is officially listed in the British Pharmacopoeia (British Herbal Medicine Association Scientific Committee 1983) as a bitter tonic and empirical evidence suggests that it acts as a carminative agent. Commission E approves the use of cut peel for loss of appetite and dyspeptic symptoms (Blumenthal et al 2000).

Weight loss

Citrus aurantium extract is growing increasingly popular as an ingredient in weight loss products, substituting for the banned ephedra in the United States. The main ingredient, synephrine, produces effects on human metabolism that could be useful for reducing fat mass in obese humans because it stimulates lipolysis, raises metabolic rate and fat oxidation through increased thermogenesis.

Currently, only two small clinical studies have been published and both suggest possible weight reduction (Preuss et al 2002); more research is required to confirm effectiveness and safety.

Superficial dermatophyte infection

The oil of bitter orange (*C. aurantium* var. *amara*) was an effective topical treatment in treatment-resistant, superficial dermatophyte infection according to a study of 60 patients (Ramadan et al 1996). Patients with tinea corporis, cruris or pedis were treated with one of three treatments based on oil of bitter orange and cure was assessed by clinical and mycological examinations. One group used a 25% emulsion of oil three times daily, the second group used 20% oil in alcohol three times daily and the third group applied pure oil once daily. Treatment

with the 25% oil emulsion was most successful and resulted in 80% of patients being cured after 1–2 weeks and 20% in 2–3 weeks. The group using the 20% oil in alcohol preparation also experienced substantial cure rates, but it took longer to achieve. Application of the undiluted oil successfully cured 33% of subjects within the first week, 60% within 1–2 weeks and 7% in 2–3 weeks. The only side effect reported was mild irritation when the undiluted oil was used.

Aromatherapy

Citrus sinensis administered in massage or via inhalation has been shown to improve mood and reduce anxiety in a range of health care settings. Lehrner et al (2000) demonstrated reduced anxiety and more positive mood compared to placebo, particularly for women, using 0.25 mL essential oil added to a diffuser in a dental waiting room (n = 72). Fitzgerald et al (2007) also showed a greater effect on mood in girls than boys in a multicultural paediatric integrative medicine clinic. Interestingly, the girls reported feeling more energetic after inhaling spearmint, whereas males felt more energetic after inhaling ginger. Overall, ginger and lavender were the least liked oils. The self-reported reductions in anxiety are supported by objective measures of autonomous function: blood pressure, respiratory and pulse rates, and skin temperature (Hongratanaworakit & Buchbauer 2007). These subjects also rated themselves as being more cheerful. Likewise Fewell et al (2007) reported sedative effects of sweet orange oil administered in a massage.

Citrus aurantium var. *dulcis*

The essential oil is used to convey warmth and happiness and improve mood (Battaglia 1997), reduce stress, and promote sleep (Miyake et al 1991). It is traditionally known as 'the oil of communication and happiness'. It is also used to improve digestion and as a carminative to relieve gastric cramping and discomfort.

Citrus aurantium var. *amara*

The essential oil is used to reduce anxiety, muscle tension and promote relaxation and best used in the bath before bedtime when treating insomnia (Battaglia 1997). It is used in cosmetics to repair broken capillaries, stimulate cell regeneration and to manage acne-prone skin.

OTHER USES

Distilled orange oil is often added to foods and beverages to enhance their flavour and to medicines to reduce the unpleasant taste.

Orange blossom water or hydrosol contains small proportions of essential oils and is used on the skin as an astringent and orally as a gastrointestinal carminative (Jeannot et al 2005). There are no terpenes in orange hydrosol, so the likelihood of causing skin irritation is significantly reduced. It is also used topically as an astringent for acne-prone skin and to calm babies and induce sleep (Bellakhdar 1997, Hmamouchi 2000).

The essential oil of *C. aurantium* var. *amara* is used as an ingredient in perfumes.

DOSAGE RANGE

Bitter orange peel products

- General dose information: 4–6 g daily of cut peel for teas or other galenical preparations used for oral administration.
- Infusion: 2 g of cut peel in 150 mL boiling water taken three times daily.
- Weight loss: bitter orange 975 mg (used with caffeine 528 mg and St John's wort 900 mg in a small double-blind study).

Essential oils

- Oral LD_{50} dose: 5 g/kg (rat).
- Dermal LD_{50} dose: >5 g/kg (rabbit) (Citrus and Allied Essences 2004).
- Oral LD_{50} dose for a 15-kg child: 83 g/kg.
- Oral LD_{50} dose for a 70-kg adult: 389 g/kg.
- Oral doses in teas and other preparations: 4–6 g/day or 2 g in 150 mL of boiled water as an infusion (American Botanical Council 1999). The inhalation LD_{50} dose has not been established.
- Topical application dose of bitter orange to skin exposed to UV rays: 1.4% of a blend. However, even when topical application is combined with inhalation, blood concentrations of *d*-limonene, a component of most citrus oils, during 20 minutes of massage is low (≤0.008 microgram/mL). It is detectable in the blood within 10 min, which represents an uptake of more than 1% of the dose administered (Fewell et al 2007).

ADVERSE REACTIONS

Skin sensitisation

Both *C. sinensis* and *C. amara* are mild skin irritants, but are considered to be low risk. Skin reactions are more likely if undiluted oils are applied directly to the skin or when used on broken or inflamed skin or when other skin pathology is present. Skin reactions are idiosyncratic and can be difficult to predict. Skin sensitisation with topically applied orange oil is largely due to the components citral and cinnamic acid and is dose dependent (Tisserand & Balacs 1995) and *d*-limonene and often occurs after long-term exposure (Verzera et al 2004).

Photosensitisation

Expressed *C. sinensis* essential oil is not normally phototoxic (Tisserand & Balacs 1995), whereas *C. amara* oil is moderately phototoxic due to its furanocoumarin content, although the risk is considered low unless higher than recommended concentrations are used or more than one potentially phototoxic oil is combined in a blend. The risk may be increased in fair-skinned individuals. Other phototoxic essential oils include *Citrus bergamia* (bergamot) and *Citrus limon* (lemon). Sensitivity to sunlight or UVB light after topical application increases in the first hour after application and declines over the following 8 h. A general caution is to avoid UV exposure for at least 12 h after topical application and use a sunscreen during this period. An early study (Zaynoun 1977) (n = 63) showed no significant differences in phototoxic reactions to

bergamot oil for eye colour, age, gender or tanning, but smaller amounts of oil produced an effect in light-skinned people. It is not clear whether this also applies to orange essential oil.

Gastrointestinal symptoms

Abdominal pain, nausea, vomiting, diarrhoea and dizziness have been reported with oral dosing (Citrus and Allied Essences 2004).

Cardiotoxicity

Bitter orange, standardised to 4–6% synephrine, demonstrated cardiovascular toxicity (ventricular arrhythmias with enlargement of QRS complex) and mortality in rats (Calapai et al 1999). The clinical significance of this finding remains unknown.

SIGNIFICANT INTERACTIONS

There are no known interactions between the essential oils and conventional medicines; however, interactions may occur with the fruit and fruit products.

Theoretically, an interaction exists for CYP 3A and P-gp substrates, as human studies indicate that the juice made from *C. aurantium* (Seville orange) inhibits CYP3A and possibly P-glycoprotein (Di Marco et al 2002, Malhotra et al 2001) — use with caution.

CONTRAINDICATIONS AND PRECAUTIONS

Do not apply essential oils to eyes or undiluted to mucous membranes. Orange essential oil is flammable and should not be vaporised near sources of heat or open flames. Therefore, candle vaporisers are not recommended. Skin sensitisation and phototoxicity are possible with the essential oils, so exposure to UV light sources should be avoided for at least 12 hours after dermal application. The risk is increased in fair-skinned individuals and when a blend that also contains other phototoxic essential oils is used.

PREGNANCY USE

Bitter orange peel and associated products are not recommended for use in pregnancy (Blumenthal et al 2000).

Orange essential oil used in recommended doses is generally safe in pregnancy, but general safety precautions apply.

PATIENTS' FAQs

What will this herb do for me?

Orange essential oil can be used in a vaporiser or massage to aid focus and concentration and facilitate communication. Neroli oil is mostly used to reduce stress and promote sleep and relaxation. In teas and tinctures, cut peel may aid digestion and relieve dyspeptic symptoms. There is some evidence that the oil may be an effective treatment for treatment-resistant fungal skin infections.

When will it start to work?

When used in aromatherapy, it usually acts soon after inhalation. When the oil or oil products are applied topically to fungal infections, results may be seen within 1–2 weeks; however, 3–4 weeks of treatment may be required. Used internally, bitter orange peel products should provide dyspeptic symptom relief quickly. Used in the bath before bedtime to promote sleep, neroli oil should produce relaxing effects within half an hour.

Are there any safety issues?

Skin irritation and phototoxicity (chemical burn) are possible after topical application of the oil if the skin is exposed to UV light such as sunlight. Use in recommended doses and do not use more than 15% of orange essential oil in a blend. Oral use of bitter orange peel products is not recommended in pregnancy and Seville orange juice can induce multiple drug interactions.

PRACTICE POINTS/PATIENT COUNSELLING

- Bitter orange peel and associated products are used to improve digestion, relieve dyspeptic symptoms and improve appetite.
- *Citrus aurantium* extract is growing increasingly popular as an ingredient in weight loss products; however, controlled studies are required to determine its safety and effectiveness.
- The oil of bitter orange (*Citrus aurantium* var. *amara*) was an effective topical treatment in treatment-resistant, superficial dermatophyte infection according to one study.
- Topical application of orange oil and bitter orange oil can induce skin sensitisation, which is more likely to occur if old orange essential oil is used because of its tendency to oxidise. Appropriate storage reduces oxidation. A patch test is recommended for atopic people or those who have a tendency to skin reactions to fragrance compounds, cosmetics or essential oils.
- Topical application of orange oil and bitter orange oil can induce photosensitivity in some individuals. After topical application, exposure to sunlight or UVB light should be avoided for at least 12 h. The risk of phototoxicity increases if high concentrations of phototoxic essential oils are used or a blend contains several phototoxic essential oils or if used by fair-skinned people.

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Passionflower

HISTORICAL NOTE Legend has it that this herb received its name because the corona resembles the crown of thorns worn by Christ during the crucifixion. A popular sedative medicine in the early 20th century, it was listed in the United States National Formulary until 1936.

COMMON NAME
Passionflower

OTHER NAMES
Apricot vine, granadilla, Jamaican honeysuckle, Maypop passion flower, passion vine, water lemon

BOTANICAL NAME/FAMILY
Passiflora incarnata (family Passifloraceae)

PLANT PARTS USED
Aerial parts, particularly leaves

CHEMICAL COMPONENTS
Flavonoids and related compounds (including apigenin, quercetin, kaempferol and chrysin), maltol, coumarin derivatives, indole alkaloids (mainly harman, harmaline, harmine), phytosterols (stigmasterol), sugars and small amounts of essential oil.

Harman
Numerous in vitro and in vivo trials have been conducted on the constituent known as harman. Some of these studies have suggested:
- mild monoamine oxidase A inhibition (Adell et al 1996)
- inhibition of HIV replication (Ishida et al 2001)
- vasorelaxant activity (Shi et al 2000)
- effects on GABA release (Dolzhenko & Komissarov 1984).

Harman is not considered to be one of the main active constituents in the herb and is not present in biologically active concentrations in the dosage range used for passionflower. As such, results obtained using isolated harman in vitro and in vivo cannot necessarily be extrapolated to the use of passionflower in humans.

Harman has also been identified in beer, and to a lesser extent in wine, both of which contain levels far in excess of those found in passionflower at therapeutic doses.

MAIN ACTIONS

Anxiolytic and sedative activity
Several in vivo studies have demonstrated the anxiolytic effects of Passiflora extract (Brown et al 2007, Della Loggia et al 1981, Dhawan et al 2001, Soulimani et al 1997). Behavioural tests in mice have also demonstrated that high doses have a sedative effect (Soulimani et al 1997).

The mechanism of action is currently unclear, as some research suggests stimulation of GABA release or an interaction with GABA receptors, and other research observes no interaction with GABA-benzodiazepine receptors (Zanoli et al 2000). One in vitro study also showed inhibition of GABA-A binding with Passiflora extract (Simmen et al 1999). An extract of the isolated flavone chrysin (2 mg/kg) was found to produce an anxiolytic effect similar to

midazolam, but the effect was observed to a lesser degree in vivo (Brown et al 2007).

Anticonvulsant

A hydro-alcoholic extract of Passiflora (Pasipay 0.4 mg/kg) has demonstrated anticonvulsant activity in vivo (Nassiri-Asl et al 2007). The extract was shown to delay onset and decrease the duration of seizures compared to placebo. It appeared to work through GABAergic and opioid pathways, however more research is needed to confirm the mechanism.

CLINICAL USE

Anxiety and nervous restlessness

Passiflora extract is a popular herb for nervousness and is most often prescribed in combination with other herbs such as valerian. A recent Cochrane review of two RCTs concluded that despite some positive findings, more trials with larger numbers of participants were needed to confirm efficacy in anxiety (Miyasaka et al 2007). One of the reviewed trials was a double-blind, randomised controlled study involving 36 outpatients diagnosed with generalised anxiety disorder (GAD). Passiflora extract was found to be as effective as oxazepam 30 mg/day over a 4-week period and better tolerated (Akhondzadeh et al 2001a).

Since then, a study published in 2008 produced encouraging results. Sixty patients were randomised to two groups and given passionflower (500 mg) or placebo 90 min before surgery (Movafegh et al 2008). Anxiety scores were significantly lower in the Passiflora group compared to the placebo group, whilst other parameters such as psychological and physiological recovery were the same for both groups.

Commission E approved passionflower for this indication (Blumenthal et al 2000).

Insomnia

Currently, in vivo evidence supports the sedative activity of Passiflora when used in high doses; however, controlled studies are not available to confirm the clinical efficacy (Soulimani et al 1997).

Cannabis, alcohol and opiate withdrawal

A randomised double-blind study involving 65 subjects with opiate addiction compared the effects of clonidine and placebo with clonidine and Passiflora extract over a 14-day period. The combination treatment of clonidine and Passiflora extract showed significant superiority for alleviating the psychological symptoms associated with withdrawal; however, no differences in physical symptoms were seen (Akhondzadeh et al 2001b).

Although no clinical studies are available for Passiflora extract, preliminary results from animal studies testing the benzoflavone moiety isolated from Passiflora has found it to be a useful adjunct during cannabis and alcohol withdrawal, reducing dependence and attenuating withdrawal symptoms (Dhawan et al 2002b, c).

OTHER USES

Traditional uses

Traditionally, passionflower has been used to treat neuralgia, generalised seizures, hysteria and insomnia. It has also been used to treat diarrhoea, dysentery and dysmenorrhoea by acting on the nervous system.

Aphrodisiac

Recent tests in mice have identified significant aphrodisiac properties associated with high doses of Passiflora extract (Dhawan et al 2003a). A benzoflavone moiety may be chiefly responsible, as tests with this isolated compound were found to increase libido and fertility of males rats after 30 days' treatment (Dhawan et al 2002a).

Antitussive and anti-asthmatic activity

P. incarnata was as effective as codeine phosphate in suppressing a sulfur-dioxide-induced cough in mice (Dhawan&Sharma2002). Passionflower (100 mg/kg) was also able to prevent dyspnoea-related convulsions in guinea pigs with acetylcholine-induced bronchospasm (Dhawan et al 2003b).

DOSAGE RANGE

- Dried herb: 2 g three to four times daily.
- Infusion of dried herb: 0.25–2 g three to four times daily.
- Fluid extract (1:1) (g/mL): 2 mL three to four times daily in 150 mL of water.
- Tincture (1:5) (g/mL): 10 mL three to four times daily.

TOXICITY

Not known.

ADVERSE REACTIONS

Drowsiness is theoretically possible with excessive doses.

One human study found that Passiflora extract has a significantly lower incidence of impairment of job performance compared with oxazepam (Akhondzadeh et al 2001b). One case reports a 34-year-old woman who developed severe nausea, vomiting, drowsiness and episodes of non-sustained ventricular tachycardia following administration of passionflower at therapeutic doses (Fisher et al 2000).

SIGNIFICANT INTERACTIONS

Controlled studies are not available; therefore, interactions are based on evidence of pharmacological activity and are theoretical.

Benzodiazepines

Additive effects are theoretically possible at high doses, although it may be a useful support during benzodiazepine withdrawal. Use with caution and monitor drug dosage — possible beneficial interaction under medical supervision.

Barbiturates

Additive CNS sedation is theoretically possible. Use with caution and monitor drug dosage — possible beneficial interaction under medical supervision.

CONTRAINDICATIONS AND PRECAUTIONS

None known.

PREGNANCY USE

Passionflower has demonstrated the ability to increase uterine contractions in an isolated rat uterus model when compared to control tissue (Sadraei et al 2003). Caution should be used until safety is better established.

PRACTICE POINTS/PATIENT COUNSELLING

- Both human and animal studies confirm passionflower has significant anxiolytic activity although more trials with larger numbers of participants are still needed to clarify its place in practice.
- One randomised study found that it has significantly less negative effects on performance than 30 mg oxazepam, yet is as effective for GAD.
- Maximal effects may require several days of regular intake.
- It is not known whether physical tolerance develops.
- One study has shown it improves psychological symptoms during opiate withdrawal when used together with clonidine.
- In practice, it is often prescribed with other herbs for stronger anxiolytic effect.

PATIENTS' FAQs

What will this herb do for me?

Passionflower may have an anxiolytic effect that can relieve restlessness and nervous tension. In higher doses, it is used for insomnia.

When will it start to work?

When being used for anxiety, it may take 3–4 weeks before significant effects are seen.

Are there any safety issues?

Overall, passionflower does not appear to impair job performance. However, it may theoretically interact with other sedative medicines when used in high doses. Other interactions are theoretically possible, so use should be monitored by a healthcare professional.

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Pelargonium

HISTORICAL NOTE *Pelargonium sidoides* DC. (Geraniaceae) is an important traditional medicine in South Africa where it has been used to treat diarrhoea, dysentery, coughs and colds, tuberculosis and gastrointestinal conditions. This and other South African traditional medicines were often referred to by their original Khoi-Khoi name *rabas*, and were amongst the first to be recorded by early explorers such as van der Stel (1685) and Thunberg (1773). The most detailed account of the value and uses of *P. sidoides* is that of Smith (1895) who listed *P. reniforme/P. sidoides* as the first of five species used in the treatment of dysentery (Brendler & van Wyk 2008). The herb was introduced to Europe by the Englishman Charles Henry Stevens and is now a popular, commercially produced herbal medicine, listed in the European Pharmacopoeia (Brendler & van Wyk 2008).

COMMON NAME
South African geranium

OTHER NAMES
Geranium, EPs 7630, Geranien, Geranium Root, Ikhubalo, Icwayiba, i-Yeza lezikali, Kalwerbossie, Pelargonien, Pelargonium Root, Rabas, Rabassam, Silverleaf geranium, Umckaloabo, Uvendle

BOTANICAL NAME/FAMILY
Pelargonium sidoides/Geraniaceae

PLANT PARTS USED
Root

CHEMICAL COMPONENTS
Oligomeric and polymeric proanthocyanidins are present in significant amounts; the putative precursors afzelechin, catechin and gallocatechin have been isolated; and highly oxygenated coumarins. Gallic acid is consistently found in high concentrations in the plant material and the minerals calcium and silica (Kolodziej 2007, Kolodziej et al 2003).

Coumarins and phenolic compounds, including simple phenolic acids and proanthocyanidins, are the principal compounds found in the special extract, EPs ® 7630 (Kolodziej 2007). Gallic acid occurs in low amounts in EPs ® 7630 (Kolodziej 2007).

MAIN ACTIONS

Antibacterial activity
Different in-vitro evaluations of the herbal preparation from the roots of *P. sidoides* and its isolated constituents demonstrated pharmacological activities including moderate, direct antibacterial effects against a panel of pathogenic bacteria that are responsible for numerous respiratory tract infections, several multi-resistant strains of *Staphylococcus aureus*, also *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis* and *Mycobacterium tuberculosis* (Kolodziej et al 2003, Lizogub et al 2007, Mativandlela et al 2006).

Clinical note — Is it* P. sidoides *or* P. reniforme*?
P. sidoides is predominantly found over large parts of the interior of southern Africa, but also occurs in coastal mountain ranges. The product may be adulterated with the very similar-looking *P. reniforme* and the two species often grow side by side. The phytochemical composition of the roots of *P. sidoides* is similar to *P. reniforme*, reflecting the close botanical relationship between the two species (Brendler & van Wyk 2008, Kolodziej 2007). Morphological distinction of the dried product is extremely difficult and chemical analysis is the only reliable method of telling them apart.

Anti-adhesion properties
It has also demonstrated an inhibition of the interaction of group A streptococci and host epithelia, thereby reducing bacterial adhesion and/or invasion of epithelia.

Immune enhancement
The root extract also exhibits notable immune modulatory capabilities. The immune modulatory activities are mediated mainly by the release of tumour-necrosis factor (TNF-alpha) and nitric oxides, the stimulation of interferon-beta, the increase of natural killer cell activity and interferon-like activity (Kolodziej et al 2003, Lizogub et al 2007). Improved phagocytosis has also been demonstrated in vitro.

ANTIVIRAL ACTIVITY
Direct antiviral activity against herpesvirus 1 and 2 has been demonstrated (Schnitzler et al 2008). *P. sidoides* extract affects the virus before penetration into the host cell and reveals a different mode of action when compared to acyclovir and might be suitable for topical therapeutic use as antiviral drug both in labial and genital herpes infection. Through induction of the interferon (IFN) system and up-regulation of cytokines, important in protecting host cells from viral infection, the herb can be expected to exhibit antiviral activity in vivo (Engler et al 2009).

OTHER ACTIONS
The liquid extract acts as an expectorant and reduces sputum production, allowing the body to expel mucus thereby making conditions less suitable for the multiplication of the bacteria and viruses.

CLINICAL USE
Most research has been conducted with a standardised liquid herbal extract of the roots of *P. sidoides* (1:8–10), extraction solvent: ethanol 11% (wt/wt) produced by Willmar Schwabe Pharmaceuticals, Karlsruhe, Germany, also known as EPs 7630 (Trademark: Umckaloabo®, marketed by Spitzner Arzneimittel, Ettlingen, Germany).

Respiratory tract infections (RTIs)

In the light of inappropriate antibiotic use and increasing drug resistance rates worldwide, the need for an alternative, effective remedy for respiratory tract conditions is crucial. *P. sidoides* has been investigated as one such medicine and represents a promising treatment for the management of RTIs. Not yet widely used in most Western countries, it has achieved widespread popularity in Germany and is approved for the treatment of acute bronchitis, acute tonsillopharyngitis and acute sinusitis.

At least 17 reports of clinical trials have been published with *P. sidoides* in the treatment of various respiratory tract infections (Brendler & van Wyk 2008). The earliest trials were conducted in the 1990s and many were observational studies. More recent studies tend to be placebo-controlled randomised trials and focused on acute bronchitis, although observational studies are still performed. The results of the individual research reports are compelling, particularly as there are no good treatment options for viral RTIs and bacterial RTIs are becoming increasingly difficult to treat.

In a 2008 Cochrane systematic review, authors evaluated data from eight randomised control trials (RCTs) and concluded that *P. sidoides* may be effective in alleviating symptoms of acute rhinosinusitis and the common cold in adults, but the findings are not yet definitive (Timmer et al 2008). They identified two RCTs that showed *P. sidoides* was effective in relieving all symptoms, and in particular cough and sputum production in adults with acute bronchitis although a third study showed that the preparation was only effective for treating sputum reduction. Similarly, *P. sidoides* was effective in resolving symptoms of acute bronchitis in two out of three paediatric studies. In acute sinusitis and the common cold, *P. sidoides* was effective in resolving all symptoms, including headaches and nasal discharge, in adults when taken for an extended time period.

Two RCTs used tablet forms and all others used liquid herbal extracts. Based on this, the authors stated that the liquid preparation (alcoholic solution) may be associated with improvement in some symptoms of acute bronchitis in both children and adults, in particular sputum production and cough, but fewer or no potential beneficial effects were seen in both children and adults taking the tablets when tested. The cause of this difference is unknown and may be due to chance or differences in constituent bioavailability or in the product's phytochemical constituents.

The same year, a review was published in *Phytomedicine* that analysed six RCTs, of which four were suitable for statistical pooling (Agbabiaka et al 2008). One study compared EPs 7630 against conventional non-antibiotic treatment (acetylcysteine); the other five studies tested EPs 7630 against placebo. All RCTs reported findings suggesting the effectiveness of EPs 7630 in treating acute bronchitis. When meta-analysis of the four placebo-controlled RCTs was conducted, the results confirmed that EPs 7630 significantly reduced bronchitis symptom scores in patients with acute bronchitis by day 7.

The most recent RCT was published in 2007 and was a randomised, double-blind, multi-centre study by Lizogub et al (2007). It demonstrated that treatment with liquid extract of *P. sidoides* significantly hastened recovery from the common cold, and markedly improved individual symptoms, most notably nasal congestion and drainage, sneezing, sore throat, hoarseness and headache. The group receiving active treatment also experienced significantly higher remission and improvement in rates of other cold-related symptoms compared to placebo, such as limb pain (95.5% vs 74%), general weakness (79% vs 35%), exhaustion (85% vs 43%) and fatigue (89% vs 60.5%) (Lizogub et al 2007). The study of 103 adults compared 30 drops (1.5 ml) of liquid herbal pelargonium three times daily to placebo for a maximum of 10 days. After this period, substantially more people receiving the herbal treatment were considered as clinically cured than the placebo group (78.8% vs 31.4%; $P < 0.0001$). All (100%) of patients receiving pelargonium judged tolerability of treatment as good or very good.

Other uses

The traditional uses of tuberous *Pelargonium* species mainly involve ailments of the gastrointestinal tract (diarrhoea and dysentery) and respiratory tract although Smith (1895) made a case for it being used as a general tonic.

Clinical note — The difficult and winding road to successful commercialisation

It is believed that the medicinal properties of *Pelargonium sidoides* were first recognised and applied by traditional tribal healers in South Africa many centuries ago. It first came to the attention of Europeans in the early 1900s, as a result of a serendipitous meeting between an Englishman, Charles Henry Stevens, and a traditional Zulu healer. In 1897, Stevens was sent to South Africa by his doctor to recover from pulmonary tuberculosis. Whilst there, he was treated by a traditional Zulu healer with a root concoction that successfully cured his condition (Bladt & Wagner 2007). Seeing the need for such a medicine back home and no doubt the commercial opportunity, Stevens called the tuberculosis treatment 'Umckaloabo' which he commercially manufactured once back in England. The treatment also became known as the 'Stevens' Cure' and caused controversy amongst the medical establishment, which sought to discredit him by labelling Stevens a 'quack'. After his death in 1942, Stevens' son sold the business to a drug manufacturer in Germany. The exact herbal ingredient in the remedy and its source was kept secret and shrouded in mystery until well into the 1970s when the plant ingredient was finally identified as *P. sidoides* by S. Bladt whilst undertaking research for her thesis in Germany (Bladt & Wagner 2007). After the conduct of scientific and clinical trials, the herb was once again commercially manufactured in Europe with great success, with an annual turnover in Germany of 80 million Deutschmark in 2006 (Brendler & van Wyk 2008).

It is also used as a gripe water for infants ('upset stomach', 'with air in the intestine'). The crushed root is mixed with water and a teaspoonful of the red infusion is taken orally (Brendler & van Wyk 2008).

The aerial parts have also been used traditionally as a wound-healing agent. This may due to their high tannin content that would contribute to its astringent effect (Kolodziej 2007).

DOSAGE RANGE

Dried herb: 0.4 g/day

According to clinical studies

- Acute treatment of respiratory tract infections.
- Adults and children over 12 years: 30 drops (1.5 ml) of liquid extract herbal pelargonium three times daily before meals for up to 10 days.
- Children aged 6–12 years: 20 drops (1.0 ml) three times per day.
- Observational studies have suggested that children under the age of 6 years may take 0.5 ml three times per day.

TOXICITY

Not known

ADVERSE REACTIONS

Overall, in all clinical and observational studies, *P. sidoides* showed a good tolerability with no serious adverse events reported (Lizogub et al 2007). A meta-analysis of eight RCTs reported that adverse events are slightly more frequent with *P. sidoides* than placebo. Besides gastrointestinal complaints such as nausea, vomiting, diarrhoea or heartburn, allergic skin reactions with pruritus and urticaria have been reported in trials (Timmer et al 2008).

De Boer et al (2007) reported that the Uppsala Monitoring Centre has, through the world health organisation (WHO) international pharmacovigilance programme, received 34 case reports of allergic reactions suspected to be associated with the use of Pelargonium extract, all originating from Germany (de Boer et al 2007). These include 12 cases of severe, life-threatening anaphylaxis. Although proof of causality is not established for each of these cases, the report describes a signal that merits further study and validation.

SIGNIFICANT INTERACTIONS

Controlled studies are not available; therefore, interactions are based on evidence of activity and are largely theoretical and speculative.

Immunosuppressant drugs

Theoretically, use of this herb may reduce the effectiveness of immunosuppressant medication — avoid until safety can be established.

CONTRAINDICATIONS AND PRECAUTIONS

People with an allergy to the geranium family of plants should avoid this herb.

PREGNANCY USE

Insufficient reliable information available to determine safety.

PRACTICE POINTS/PATIENT COUNSELLING

- *P. sidoides* is a traditional herbal medicine originating from South Africa and now extremely popular in Europe, particularly Germany.
- The herb demonstrates antibacterial activity and enhances immune function, also activity against herpesvirus 1 and 2.
- Observational and randomised studies suggest that it may be useful in the acute treatment of respiratory infections, particularly bronchitis.
- It appears to hasten recovery from the common cold, reduce symptoms and improve associated fatigue and weakness and may have a role in the acute treatment of other, uncomplicated respiratory infections.
- It is generally well tolerated; however, gastrointestinal side effects and allergic skin reactions have been reported with use.

PATIENTS' FAQs

What will this herb do for me?

Pelargonium sidoides can enhance immune function and hasten recovery from respiratory tract infections such as bronchitis, whilst improving symptoms.

When will it start to work?

When used as acute treatment of the common cold, symptom relief may be noticeable within 3 days and significant after 5 days.

Are there any safety issues?

It is generally well tolerated; however; gastrointestinal side effects and allergic skin reactions have been reported with use.

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Peppermint

HISTORICAL NOTE The written record of mint dates back to an ancient Greek myth in which the Greek god Pluto was said to have affections for a beautiful nymph named Minthe. His jealous wife Persephone cast a spell on the nymph, transforming her into a plant. When Pluto could not reverse the spell, he gave her a sweet scent that would emanate throughout the garden (Murray & Pizzorno 1999). Peppermint has been used medicinally for generations as a digestive aid and carminative. More recently, enteric-coated peppermint oil capsules have been widely prescribed for the relief of irritable bowel syndrome (IBS).

BOTANICAL NAME/FAMILY

Mentha × *piperita* (family [Labiatae] Lamiaceae)

PLANT PARTS USED

Leaf or stem — essential oil is distilled from the aerial parts.

CHEMICAL COMPONENTS

Peppermint leaves contain about 2.5% essential oil, 19% total polyphenolic compounds, 12% total flavonoid compounds (eriocitrin, luteolin-7-*O*-rutinoside and hesperidoside) and 7% total hydroxycinnamic compounds (including rosmarinic acid) (Duband et al 1992). The biochemistry, organisation and regulation of essential oil metabolism in the epidermal oil glands of peppermint have been defined, and research is underway to create 'super' transgenic peppermint plants with improved oil composition and yield (Wildung & Croteau 2005).

Essential oil

Over 100 constituents have been identified in peppermint oil. The principal constituents are menthol (35–55%), menthones (10–35%), isomenthone, menthyl acetate, menthofuran and cineole. To comply with the European Pharmacopoeia, the oil must not contain more than 4% pulegone and not more than 1% carvone.

MAIN ACTIONS

The actions of the leaf as an infusion or liquid extract are largely dependent on the essential oil content. Other compounds, such as the flavonoids, also contribute to the overall activity, especially the antioxidant and anti-allergic activities. Peppermint oil is relatively rapidly absorbed after oral administration and eliminated mainly via the bile (Grigoleit & Grigoleit 2005a).

Antispasmodic

Peppermint oil, ethanol extracts and flavonoids isolated from the leaf have all been shown to have antispasmodic (spasmolytic) effects in vitro (ESCOP 1997) with the effect mediated via smooth muscle calcium channels (Hills & Aaronson 1991). Newer research has shown that menthol induces Ca^{2+} ion influx in a subset of sensory neurons from dorsal root and trigeminal ganglia, due to the activation of TRPM8, a Ca^{2+}-permeable cold-activated member of the TRP superfamily of cation channels. Although menthol has been shown to induce Ca^{2+} release from intracellular stores in several TRPM8-expressing cell types, which would suggest that TRPM8 functions as an intracellular Ca^{2+} release channel, a TRPM8-independent pathway of Ca^{2+} release, originating from the endoplasmic reticulum and the Golgi compartments, has recently been postulated (Kim et al 2009, Mahieu et al 2007).

In healthy volunteers, intragastric administration of a dose equivalent to 180 mg peppermint oil reduced intraoesophageal pressure within 1–7 min of infusion (Kingham 1995), while in nine human studies involving 269 subjects, peppermint oil produced substantial spasmolytic effects on the smooth muscles of the gastrointestinal tract when used topically (intraluminal) or orally in doses of 0.1–0.24 mL (Grigoleit & Grigoleit 2005b). Enteroplant, an enteric-coated capsule containing 90 mg peppermint and 50 mg caraway oil, has also been shown to act locally in the stomach and duodenum to produce smooth muscle relaxation (Micklefield et al 2003). Peppermint oil has also been shown to have similar antispasmodic activity on the colon to the Chinese herbal medicine shakuyaku-kanzo-to (TJ-68), as observed by direct observation during colonoscopy (Ai et al 2005). Moreover, while investigating the effects of herbal extracts on the frequency and amplitude of slow waves in the small intestine, it was found that peppermint leaf reduces the frequency but leaves the amplitude unchanged (Sibaev et al 2006).

Carminative

Peppermint has a carminative activity, which refers to its ability to relax the gastrointestinal sphincters. Carminatives are thought to alleviate symptoms of bloating and gas by facilitating eructation and passage of flatus. The classic carminatives are essential oils, such as spearmint and peppermint. Studies from the 1950s on the effect of carminatives on the gut suggest that they work by inducing relaxation of the lower oesophageal sphincter (LES) (Massey 2001). A later study has shown that peppermint oil canalised into the gall bladder and duodenal areas was able to counteract morphine hydrochloride-induced constriction of the sphincter of Oddi (Giachetti et al 1988).

Choleretic

Choleretic activity has been demonstrated for peppermint tea, flavonoids and the essential oil in dogs and rats (ESCOP 1997). Hydrophilic compounds may contribute to the gastrointestinal effects, with aqueous extracts from peppermint leaves having antiulcerogenic and choleretic effects (Grigoleit & Grigoleit 2005c, Van Rensen 2004). Peppermint oil has been shown to have a relaxing

effect on the gall bladder and small intestine, producing complete inhibition of gall bladder emptying and prolonged orocaecal transit time comparable to that produced by *N*-butylscopolamine (Goerg & Spilker 2003).

Antimicrobial

Antibacterial

Peppermint oil has been shown to have a significant antibacterial activity (Mimica-Dukic et al 2003), as has the juice of peppermint leaves (Rakover et al 2008, Saeed & Tariq 2005). Peppermint oil has been shown to inhibit *Helicobacter pylori*, *Staphylococcus aureus* (Betoni et al 2006, Imai et al 2001, Mohsenzadeh 2007, Yadegarinia et al 2006), *Escherichia coli* (Mohsenzadeh 2007, Pattnaik et al 1995, Yadegarinia et al 2006), *Salmonella enteritidis*, *Listeria monocytogenes* and multiresistant strains of *Shigella sonnei* and *Micrococcus flavus* (Mimica-Dukic et al 2003). When investigating anti-*Staphylococcus aureus* activities, synergistic effects between peppermint extract and various antimicrobial drugs were found (Betoni et al 2006).

Fungistatic, fungicidal

Peppermint is also fungistatic and fungicidal (Pattnaik et al 1996, Positive Health News 1998) with its activity against *Trichophyton tonsurans*, *Candida albicans* and other micromycetal food poisoning, plant, animal and human pathogens being considerably greater than the commercial fungicide bifonazole but lower than that of *Thyme* spp (Mimica-Dukic et al 2003, Sokovic et al 2009, Yadegarinia et al 2006). Fungicidal activity similar to lavender and clove oil was reported for peppermint oil against *Trichophyton mentagrophytes* when used in combination with salt and heat (Inouye et al 2007). Peppermint oil showed high antifungal activity against *Candida albicans* (Yigit et al 2008), with one study reporting a 74% *Candida albicans* (strain CA I) biofilm reduction due to the effects of peppermint oil (Agarwal et al 2008). Moderate antifungal activity was observed for peppermint oil against *Rhizopus stolonifer*, *Botrytis cinerea*, *Aspergillus niger*, *Aspergillus candidus*, *Penicillium* spp and *Fusarium culmorum* (Behnam et al 2006, Magro et al 2006). Moreover, peppermint oil at various concentrations has shown to inhibit aflatoxin B production by 85–90% when evaluated for activity against *Aspergillus parasiticus* and *Aspergillus flavus* (Bluma et al 2008). Peppermint oil and its main constituent menthol have also been shown to have significant antibacterial, antifungal and antiplasmid activity and to potentiate the antibiotic effect of oxytetracycline (Schelz et al 2006).

Peppermint oil has further been shown to have a significant antimycobacterial activity in vitro, and inhalation of peppermint oil has been successfully used as a supplement to combined multidrug therapy for pulmonary tuberculosis (Shkurupii et al 2002). In a recent study, peppermint oil showed stronger antimicrobial and antibiofilm properties than chlorhexidine against *Streptococcus mutans* and *Streptococcus pyogenes* (Rasooli et al 2008).

Antiviral

Peppermint oil also has virucidal activity against herpes simplex virus (HSV)-1 and -2, including activity against an acyclovir-resistant strain of HSV-1 (ACV_{res}) with a 50% inhibitory concentration determined at 0.002 and 0.0008% for HSV-1 and HSV-2, respectively. The oil was also found to affect the virus before, but not after, penetration into the host cell (Schuhmacher et al 2003). Aqueous extract (Geuenich et al 2008, Nolkemper et al 2006) and 80% ethanolic extract of peppermint (Reichling et al 2008) at maximum noncytotoxic concentrations reduced plaque formation of HSV-1, HSV-2 and ACV_{res} significantly following exposure of free virions as well as host cells to the extracts prior to infection.

Insecticidal

Peppermint oil showed moderate repellent activity against *Culex pipiens* (Erler et al 2006), and menthol and its derivatives showed mosquitocidal activity against *Culex quinquefasciatus*, *Aedes aegypti* and *Anopheles tessellatus* (Samarasekera et al 2008). Peppermint oil was shown to only exert some repellence against head lice (*Pediculus humanus* var. *capitis*), which was due to the slippery nature of the oil rather than specific repellent activity (Canyon & Speare 2007). However, a combination product of 5% eucalyptus and 5% peppermint oil in 50% ethanol showed effectiveness against the head lice (Gonzalez Audino et al 2007).

Antiparasitic

Aqueous extracts of peppermint showed activity against gastrointestinal nematodes in goats and pigs (De Almeida et al 2007, Lans et al 2007). In vitro, dichlormethane extracts, but not water extracts, of peppermint showed antigiardial activity by causing alterations on the plasma membrane surface of the parasite and inhibiting its adhesion (Vidal et al 2007).

Anti-allergic

A 50% hydroethanolic extract of peppermint leaves inhibited chemically induced histamine release from rat peritoneal mast cells in vitro. The peppermint extract was also shown to reduce nasal symptoms (sneezing and nasal rubbing) in rats with experimentally induced allergic rhinitis. Significant inhibition of sneezing and nasal rubbing was observed at oral doses of 300 and 1000 mg/kg, respectively (Inoue et al 2001).

The flavonoid luteolin-7-*O*-rutinoside isolated from the aerial parts of peppermint has been shown to inhibit histamine release from rat peritoneal mast cells in a dose-dependent manner (100–300 mg/kg) and to reduce antigen-induced allergic nasal symptoms (Inoue et al 2002), although it would be difficult to achieve such doses of luteolin with a commercially available peppermint extract or oil. An extract of the whole herb, however, may be beneficial in alleviating nasal symptoms associated with allergic rhinitis in association with other medicines.

Antioxidant

The polyphenolic compounds in peppermint, such as luteolin-7-*O*-rutinoside, eriocitrin and rosmarinic acid, have been shown to have antioxidant and free radical scavenging activity (Sroka et al 2005). Peppermint oil and its constituents menthone and isomenthone exert antioxidant activity (Mimica-Dukic et al 2003). Interestingly, peppermint and lemon balm exerted the strongest antioxidant and radical scavenging effects when examining all individual herbs from a herbal combination preparation (STW5 — Iberogast: 9 plant extracts from *Mentha piperita*, *Iberis amara, Chelidonii herba*, *Cardui mariae fructus*, *Melissae folium*, *Carvi fructus*, *Liquiritiae radix*, *Angelicae radix*, *Matricariae flos*) (Germann et al 2006, Schempp et al 2006).

Stimulant

Intraperitoneal and intravenous injections of peppermint oil and its constituents, 1,8-cineol, menthone, isomenthone, menthol, pulegone, menthyl acetate and caryophyllene, dramatically increased ambulatory activity in mice, which may explain the traditional use of peppermint for mental fatigue (Umezu & Morita 2003, Umezu et al 2001). A recent study suggests that this effect exerted by menthone is mediated via dopamine (Umezu 2009). Inhalation of peppermint oil has also been shown to have a stimulant effect on mice in a forced swimming test, with the effect remaining when over-agitation was induced by intraperitoneal caffeine (Lim et al 2005).

Coolant

Peppermint oil interacts with smooth muscle calcium channels (Hills & Aaronson 1991). In the peripheral nerves, this effect may be responsible for the characteristic cooling sensation experienced on oral ingestion of mint.

Analgesic

Peppermint and caraway oil have been shown to synergistically modulate postinflammatory visceral hyperalgesia in a rat model (Adam et al 2006). A significant analgesic effect, with a reduction in sensitivity to headache, was observed in a double-blind, placebo-controlled, randomised, 7-day cross-over study that used a combination of peppermint oil and ethanol applied externally in 32 healthy males undergoing artificial pain stimulation (Gobel et al 1994).

PROTECTS AGAINST RADIATION-INDUCED TOXICITY

Mentha piperita protects against radiation-induced lethality, lipid peroxidation and DNA damage (Jagetia 2007) through its antioxidant and free radical scavenging activities (Samarth et al 2006b). The same authors suggest that these activities are also responsible for a significant reduction in the number of lung tumours observed in mice following oral administration of peppermint extract (Samarth et al 2006a). It has also been reported that peppermint protected against radiation-induced haematopoietic damage in bone marrow of mice by increasing erythropoietin levels (Samarth 2007). In prostate cancer cells, menthol-induced cell death was not associated with Ca^{2+} influx pathways (Kim et al 2009).

OTHER ACTIONS

A spray-dried peppermint infusion has been found to be mildly diuretic and produce weak sedative action in several tests when administered orally to mice (Della et al 1990). Peppermint tea has been found to significantly increase follicle stimulating hormone (FSH) and luteinising hormone (LH) levels and reduce total testosterone levels in rats (Akdogan et al 2004). Concomitant topical exposure to low concentrations of peppermint oil reduced the percutaneous penetration of benzoic acid; however, with increased peppermint oil doses, penetration of benzoic acid increased (Nielsen 2006). Peppermint extract was shown to reduce the side effects of arsenic-induced hepatopathy (Sharma et al 2007). In a recent study, peppermint oil displayed acetylcholinesterase and butyrylcholinesterase inhibitory activities, which was more than the activity exerted by individual components of the oil (Orhan et al 2008).

CLINICAL USE

In practice, peppermint and its derivatives are used in many forms and administered by various routes. This review will focus only on those methods that are commonly used by the public and preparations that are available over the counter (OTC), such as oral dose forms, topical applications and inhalations.

IBS

There have been several studies examining the effects of peppermint oil in the treatment of IBS (Dew et al 1984, Rees et al 1979). Newer studies have tended to use pH-triggered, enteric-coated peppermint oil capsules that prevent dissolution of the capsules until they have reached the small intestine, and release into the colon is extended over 10–12 hours (Grigoleit & Grigoleit 2005c). Enteric coating allows administration of a higher dose than would otherwise be possible to tolerate and, importantly, avoids the risk of excessively relaxing the lower oesophageal sphincter and causing reflux.

A critical review and meta-analysis of peppermint oil for IBS performed in 1998, which included five double-blind trials, concluded that peppermint oil is efficacious for symptom relief in IBS but that there was insufficient evidence to claim benefit beyond reasonable doubt (Pittler & Ernst 1998). A 2005 review identified 16 clinical trials investigating peppermint oil in IBS. Of these, eight of 12 placebo-controlled studies showed statistically significant effects in favour of peppermint oil, with an average response for 'overall success' being 58% for peppermint oil and 29% for placebo. Three studies that compared peppermint oil to smooth muscle relaxants showed no difference between these treatments (Grigoleit & Grigoleit 2005a). Since then, one randomised double-blind study involving 57 patients with IBS without bacterial overgrowth found that treatment with two enteric-coated capsules of peppermint oil twice

daily (Mintoil) for 4 weeks produced statistically significant improvement in diarrhoea, abdominal bloating, constipation, lower abdomen pain, pain on defecation, feeling of incomplete evacuation and difficulty on evacuation (Cappello et al 2006, 2007). One recent review showed that peppermint oil and fibre were more effective than placebo in the treatment of IBS (Ford et al 2008). Moreover, another recent review concluded that peppermint oil seems to be the most promising agent for the treatment of IBS (NNT 2.5). Although this conclusion was only based on the results of four trials (n = 400), there was only little heterogeneity between the three high quality trials and no significant adverse effects were reported (Jones 2008). Two reviews summarise the evidence for pharmacological interventions for recurrent abdominal pain and IBS in children (Banez 2008, Huertas-Ceballos et al 2008); however, both of these reviews refer to only one trial so far conducted in children, thus highlighting the need for more research in the area. In the cited, randomised, double-blind, controlled trial of 42 children with IBS, treatment with enteric-coated peppermint oil capsules reduced the severity of the pain in 75% of the children (Kline et al 2001).

Bacterial overgrowth of the small intestine is associated with a number of functional somatic disorders, including IBS, fibromyalgia and chronic fatigue syndrome (CFS). There have been two reports of successful treatment of IBS due to intestinal overgrowth with enteric-coated peppermint oil capsules. This clinical effect may in part be associated with the antimicrobial activities of peppermint oil (Gaby 2003, Logan & Beaulne 2002).

Clinical note — Pathophysiology of IBS

The pathophysiology of IBS is poorly understood, but it is believed to occur when the intestinal muscles are contracting faster or more slowly than normal. Colonic contractions cause abdominal pain, cramping, wind and diarrhoea or constipation. It has been proposed that IBS may result from dysregulation of gastrointestinal motor and enhanced sensory functions, as modulated by the central nervous system (CNS). However, clinical and laboratory investigations have failed to uncover any histological, microbiological or biochemical abnormalities in patients with IBS. Patients with IBS demonstrate increased motility and abnormal contractions of the intestinal muscles when faced with an emotionally or physically stressful situation (Greenberg et al 2002). It is likely that IBS is also associated with dietary habits, poor upper digestion and intestinal dysbiosis (bacterial overgrowth of the bowels).

Common symptoms of IBS are (Greenberg et al 2002) as follows:

- cramping pain in the lower abdomen
- bloating and excess gas (wind)
- changes in bowel habits
- diarrhoea or constipation, either one dominant or both alternating
- immediate need for a bowel movement on awakening or during or after meals
- relief of pain after bowel movements
- feeling of incomplete emptying after bowel movements
- mucus in the stool.

Dyspepsia

A two-way crossover study with 10 healthy male volunteers showed that peppermint oil enhances gastric emptying during the early phase (decrease in T lag and beta constant), suggesting the potential use of peppermint oil in functional gastrointestinal disorders (Inamori et al 2007).

In a systematic review of herbal medicines for functional dyspepsia, Coon & Ernst (2002) found 17 randomised clinical trials, 9 of which involved peppermint and caraway combination preparations, with 60–95% of patients reporting improvements in symptoms.

An enteric-coated capsule (Enteroplant) that contains 90 mg peppermint oil (WS-1340) and 50 mg caraway oil (WS-1520) has been shown in a double-blind, placebo-controlled, multicentre trial with 45 patients to significantly improve symptoms of nonulcer dyspepsia. Nearly 90% of patients experienced a reduction in pain, and after 4 weeks, nearly 95% had improved their Clinical Global Impression scores. Before the start of treatment, all patients in the test preparation group reported moderate to severe pain, while by the end of the study 63.2% of these patients were free of pain. The peppermint and caraway oil combination was well tolerated (May et al 1996).

Since then, there have been three further randomised placebo-controlled trials of this particular peppermint–caraway oil combination. In one trial with 223 patients with nonulcer dyspepsia and IBS, the peppermint oil combination was found to significantly reduce pain compared to placebo ($P < 0.001$) (Freise & Kohler 1999). In a further study of 96 outpatients, the same peppermint formulation was found to significantly improve symptoms of functional dyspepsia. After 4 weeks, the average intensity of pain was reduced by 40% versus baseline in the active group and by 22% in the placebo group. The peppermint combination also reduced pressure, heaviness and fullness (May et al 2000). A subgroup analysis from this study revealed that *Helicobacter pylori*-positive patients had a substantially better treatment response, although those who were negative to *H. pylori* also showed significant improvements compared to those receiving placebo (May et al 2003). In a further double-blind placebo-controlled trial, the same oil combination was found to significantly improve disease-specific quality of life (QOL), as measured by the validated Nepean Dyspepsia Index compared to placebo (Holtmann et al 2003).

The same peppermint and caraway oil combination has been compared with cisapride (Prepulsid), which increases the LES pressure, thereby reducing the risk of reflux. Cisapride is also used to treat IBS dominated by constipation but has been linked to serious cardiac arrhythmias and should be used with caution. In the 4-week study, the peppermint and

caraway oil combination (Enteroplant, 2 capsules daily) was shown to be as effective as cisapride in reducing both the magnitude and the frequency of pain. Physicians rated the two treatments comparable in regard to other dyspeptic symptoms, in addition to intestinal and extraintestinal autonomic symptoms. Corresponding results were also found in *H. pylori*-positive patients and patients who initially presented with intense epigastric pain in the two treatment groups. Both medications were well tolerated (Madisch et al 1999).

A combination herbal preparation (STW5 — Iberogast) that includes peppermint leaf extract and eight other plant extracts (*Iberis amara*, *Chelidonii herba*, *Cardui mariae fructus*, *Melissae folium*, *Carvi fructus*, *Liquiritiae radix*, *Angelicae radix* and *Matricariae flos*) has been demonstrated to significantly relieve dyspepsia in a number of randomised controlled trials (RCTs), including a meta-analysis of three trials (Melzer et al 2004), with a fourth RCT showing similar effects to cisapride (Rosch et al 2002). In a newer study, it was shown that STW5 lowered gastric acidity as effectively as commercial antacid preparations (i.e. Rennie, Talcid and Maaloxan), prevented secondary hyperacidity more effectively and additionally inhibited serum gastrin levels in rats (Khayyal et al 2006).

Diffuse oesophageal spasm

Diffuse oesophageal spasm (DES) is a relatively rare motor disorder. Associated manometric abnormalities may include hypertensive and repetitive contractions. The LES may also be hypertensive. Although LES relaxation with deglutition is generally normal, disturbances in LES function are often seen. These abnormalities are, however, not required for the diagnosis (Massey 2001). In a study of eight DES patients with chest pain or dysphagia, peppermint oil had no effect on LES pressures or contractile pressures and durations in the oesophagus, yet completely eliminated simultaneous oesophageal contractions in all patients ($P < 0.01$). The number of multiphasic, spontaneous and missed contractions also improved. Two of the eight patients had their chest pain resolved after taking the peppermint oil (Pimentel et al 2001).

Antispasmodic

The results from a randomised, double-blind, double-dummy, controlled trial suggest that the antispasmodic properties of peppermint oil can be utilised intraluminally during upper endoscopy with superior efficacy and fewer side effects than hyoscine-*N*-butylbromide (Buscopan) administered by intramuscular injection (Hiki et al 2003a, 2003b). The peppermint oil solution was subsequently used to successfully extend an endoscope past an area of severe antral stenosis in a case that was unresponsive to Buscopan. A further study of 383 patients receiving double-contrast barium enemas, which compared peppermint oil in the barium, peppermint oil in the enema tube, Buscopan and no treatment, found that peppermint oil in the barium or the enema tube could be safely and effectively used instead of Buscopan and that the oil had a stronger antispasmodic effect in the caecum and the ascending colon than a Buscopan injection (Asao et al 2003). Similarly, orally administered peppermint oil was an effective and safe antispasmodic agent for double-contrast barium meal examination in a controlled study with 420 participants (Mizuno et al 2006). In another study ($n = 40$), peppermint oil (20 mL, 1.6%) was effective and safe in inhibiting duodenal motility during endoscopic retrograde cholangiopancreatography, but additional administration was recommended for future procedures. The effect was identical to that of glucagon (Yamamoto et al 2006).

Headache

A solution of 10% peppermint oil in ethanol has been shown in a randomised, placebo-controlled, double-blind, crossover study to efficiently alleviate tension-type headache. The study analysed 164 headache attacks in 41 patients of both sexes ranging between 18 and 65 years of age, suffering from tension-type headache. The peppermint oil was spread largely across forehead and temples and repeated after 15 and 30 min. Using a headache diary, the headache parameters were assessed after 15, 30, 45 and 60 min. Compared with the application of a placebo, the peppermint oil significantly reduced the intensity of the headache after 15 min ($P < 0.01$). The analgesic effect of the peppermint oil was comparable to 1000 mg paracetamol (acetaminophen). Simultaneous ingestion of 1000 mg of paracetamol and application of 10% peppermint oil in ethanol solution led to a slight additive effect (Gobel et al 1996).

Postoperative nausea

Inhalation of peppermint oil vapours has been shown in a study to reduce postoperative nausea in gynaecological patients in a placebo-controlled trial in which patients were free to inhale peppermint oil as frequently as desired (Tate 1997). A hot peppermint oil compress is used in China to prevent abdominal distension in postoperative gynaecological patients (Feng 1997). In another placebo-controlled trial, a reduction in postoperative nausea was seen equally with inhalation of isopropyl alcohol, peppermint oil or saline, with the authors attributing the effect to the controlled breathing used during inhalation (Anderson & Gross 2004).

Respiratory tract infections

Peppermint and menthol have an established tradition in the treatment of respiratory infections. Chest rubs containing menthol are frequently used to treat coughs and bronchitis. Inhalation of various antiseptic and anti-inflammatory essential oils is often used in the treatment of respiratory infections, including bronchitis (Shubina et al 1990). In a recent study conducted with 18 healthy volunteers, it was shown that menthol inhalation did not affect nasal mucosal temperature and nasal airflow but supported the fact that menthol leads to direct stimulation of cold receptors modulating the cool sensation, thus inducing a feeling of clear and open nasal passages (Lindemann et al 2008).

Peppermint oil has been found to have a pronounced antimycobacterial effect in vitro, and long-term use of peppermint oil in a humidifier has been used in Ukraine as an adjunctive treatment to multidrug therapy for pulmonary tuberculosis (Shkurupii et al 2002). A more recent study shows that inhaling peppermint oil by patients with infiltrative pulmonary tuberculosis in the penitentiary system was most effective in the phase of resorption of infiltrates and/or closure of decay cavities (Shkurupii et al 2006).

Enhance cognitive performance

A combination of peppermint oil, eucalyptus oil and ethanol was shown in a crossover double-blind study to increase cognitive performance and promote relaxation in 32 healthy subjects (Gobel et al 1994). Peppermint odour has also been shown to reduce daytime sleepiness (Norrish & Dwyer 2005) and fatigue and to improve mood (Goel & Lao 2006), as well as significantly improve performance in difficult tactile tasks (Ho & Spence 2005) and promote a general arousal of attention with improved typing speed and accuracy (Barker et al 2003). Similarly, in a recent study with healthy volunteers (n = 144), peppermint oil inhalation enhanced memory and alertness (Moss et al 2008).

OTHER USES

Peppermint or pure menthol is commonly used in heat rub ointments for arthritis, fibromyositis, tendonitis and other musculoskeletal conditions. Commission E approved peppermint oil externally for neuralgia and myalgia (Blumenthal et al 2000). A case report describes the treatment of postherpetic neuralgia with the direct application of undiluted peppermint oil containing 10% menthol to the affected area. The pain relief persisted for 4–6 h after application of the oil. At a 2-month follow-up, the patient had only minor side effects and continued to use the medication (Davies et al 2002). An aromatherapy acupressure intervention using peppermint oil displayed positive effects on hemiplegic shoulder pain, compared to acupressure alone, in patients with stroke (Shin & Lee 2007).

An oral spray or gargle containing a range of essential oils including peppermint oil is reported to reduce snoring in one double-blind study (Prichard 2004). A mixture of tea tree, peppermint and lemon oil seemed effective in reducing malodour and volatile sulphur compounds in intensive care unit patients (Hur et al 2007).

Two studies conducted with breastfeeding women found that topical application of peppermint water and peppermint gel prevented nipple cracks and associated pain more effectively than lanolin and placebo (Melli et al 2007a, 2007b).

A small study (n = 44) conducted with patients undergoing breast cancer treatment showed that 18 of them (41%) chose peppermint and neroli hydrolat spray over plain water spray to manage their hot flashes (Dyer et al 2008).

Antimicrobial and antibiofilm properties of peppermint oil against *Streptococcus mutans* and *Streptococcus pyogenes* were evident, when an in-vivo study with healthy volunteers showed that brushing teeth with peppermint oil-blended toothpastes was more effective than using a chlorhexidine mouthwash (Shayegh et al 2008).

Traditional uses

Traditionally, peppermint was believed to increase libido and used to stop hiccups, relieve pain in childbirth, reduce bleeding and treat menorrhagia (Fisher & Painter 1996). It was also used externally to repress lactation, to treat dermatological conditions, as a mouthwash for painful gums and mouth and applied to the temples to relieve headaches.

DOSAGE RANGE

Leaf

- Infusion: 3–6 g three times daily (Blumenthal et al 2000).
- Liquid extract (1:2): 1.5–4.5 mL/day.

These dosages are for adults; adjust according to size for children.

Essential oil

- Digestive disorders: 0.2–0.4 mL three times daily in dilute preparations or in suspension (ESCOP 1997).
- IBS: 0.2–0.4 mL three times daily in enteric-coated capsules or tablets (Dew et al 1984, Rees et al 1979).
- Inhalation: 3–4 drops added to hot water.
- Lozenge: 2–10 mg.
- External use (for analgesic, anaesthetic or antipruritic activity): 0.1–1.0% m/m (ESCOP 1997).
- External use (counterirritant): 1.25–16% m/m (ESCOP 1997).

ADVERSE REACTIONS

A single dose of 4000 mg/kg of a spray-dried infusion did not produce any macroscopic signs of toxicity in mice (Della et al 1990). Peppermint oil taken orally has been shown to be well tolerated at the commonly recommended dosage but may cause significant adverse effects at higher doses (Kligler & Chaudhary 2007).

Short-term and subchronic oral studies reported brain lesions in rats that were given very large doses of peppermint oil containing pulegone, pulegone alone or large amounts (>200 mg/kg/day) of menthone. Pulegone is also a recognised hepatotoxin, and large doses of peppermint oil have been shown to be hepatotoxic in cultured human hepatoma cells (Vo et al 2003). Peppermint oil was negative in an Ames test and a mouse lymphoma mutagenesis assay but gave equivocal results in a Chinese hamster fibroblast cell chromosome aberration assay. There is a case report of acute lung injury following intravenous injection of peppermint oil (Behrends et al 2005).

Although sensitisation to peppermint oil and/or its constituents has been reported, a solution containing 8% peppermint oil was shown not to be a sensitiser (Nair 2001). Cases of allergic contact dermatitis to peppermint and menthol have been reported following intraoral application (Morton et al 1995, Tamir et al 2005), with one case reporting

vulval allergic contact dermatitis following long-term (6 years) high oral consumption of peppermint tea (Vermaat et al 2008). Moreover, the application of a transcutaneous patch (Foti et al 2003) or foot spray (Kalavala et al 2007) caused allergic contact dermatitis. However, the incidence of allergic contact dermatitis due to peppermint and its components is low considering its widespread use and seems to be more common in patients with a history of allergic reactions (Kalavala et al 2007, Vermaat et al 2008). As long as the pulegone content is kept to a minimum, peppermint oil and peppermint extract are considered to have a very good safety profile.

SIGNIFICANT INTERACTIONS

Controlled studies are not available; therefore, interactions are based on evidence of activity and are largely theoretical and speculative.

Felodipine

Peppermint oil has been shown to increase the oral bioavailability of felodipine in animal studies (Dresser et al 2002b) — use this combination with caution.

Simvastatin

Peppermint oil has been shown to increase the oral bioavailability of simvastatin in animal studies (Dresser et al 2002b). Observe the patient and monitor drug requirements — possible beneficial interaction.

Cyclosporin

Peppermint oil has been shown to increase the oral bioavailability of cyclosporin in animal studies (Dresser et al 2002b) — avoid concurrent use, unless under medical supervision.

Drugs metabolised by CYP3A4 liver enzyme

Peppermint may increase the oral bioavailability of certain drugs by inhibition of CYP3A4-mediated drug metabolism, which has been demonstrated in vitro but not in test animals (Dresser et al 2002a, Maliakal & Wanwimolruk 2001). Although these studies seem to suggest that peppermint may modulate drug-metabolising enzymes, the clinical significance of this is unknown and requires further investigation.

CONTRAINDICATIONS AND PRECAUTIONS

Hypersensitivity to peppermint oil (Morton et al 1995)

Non-enteric-coated peppermint may be best avoided in patients with gastro-oesophageal reflux symptoms (McKay & Blumberg 2006). Avoid chewing enteric-coated capsules as it may cause heartburn (Liu et al 1997). Avoid the use of peppermint oil on the face of infants and small children. Capsules containing peppermint oil are contraindicated in biliary duct occlusion, gall bladder inflammation and severe liver damage (Blumenthal et al 2000). Similarly, caution has been urged in patients with hiatal hernia and kidney stones (McKay & Blumberg 2006).

PREGNANCY USE

Safe dosages in pregnant women have not been determined; however, external use is likely to be safe.

PRACTICE POINTS/PATIENT COUNSELLING

- Peppermint oil and/or peppermint leaf extracts can be used for IBS, dyspepsia, flatulence, intestinal colic and biliary disorders. Note, however, that peppermint oil is contraindicated in inflammation of the gall bladder and severe liver disease.
- Although enteric-coated peppermint oil capsules may prevent side effects such as reflux and allow higher doses to be used, traditional extracts of peppermint, including hydroethanolic extracts and infusions, may also be effective.
- Peppermint leaf extract combines well with chamomile, caraway, licorice, lemon balm, angelica, St Mary's thistle and the bitter candytuft (*Iberis amara*) in the treatment of functional dyspepsia (Madisch et al 2001).
- Peppermint oil can be used as an inhalation or chest rub for coughs, sinusitis and bronchitis. Commission E approved peppermint oil for internal use in the treatment of respiratory tract inflammation (Blumenthal et al 2000), and hot peppermint leaf infusion is used as a diaphoretic tea in the treatment of colds and influenza.
- Peppermint oil can be inhaled to reduce nausea and may enhance cognitive performance and tactile tasks.
- Ten per cent peppermint oil in ethanol solution can be applied externally for tension headaches and over affected areas for postherpetic neuralgia.

PATIENTS' FAQs

What will this herb do for me?

Peppermint is a safe herb for gastrointestinal disorders, including dyspepsia and IBS. It is also safe for children, particularly as a herbal tea.

When will it start to work?

Peppermint will generally have an immediate effect, with the condition continuing to improve with long-term use.

Are there any safety issues?

Concentrated peppermint oil preparations may theoretically interact with a number of different medications. It is unlikely that any interaction will occur with peppermint tea or simple liquid extracts. Avoid the use of peppermint oil on the face of infants and small children.

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Perilla

HISTORICAL NOTE Perilla is an annual plant native to Eastern Asia. It was introduced to Japan from China and is now cultivated extensively in Japan, India and Korea. The seed is mainly used for its high oil content, and the leaves of *Perilla frutescens* var. *crispa* are used as a vegetable and food colouring in gourmet cooking. The salty umeboshi plum is coloured by the addition of special red perilla leaves. In China, perilla has been used to reduce the risk of food poisoning by cooking seafood with the leaf (Bensky & Gamble 1986). In recent times, certain compounds (monoterpenes) isolated from the oil are being investigated as an anticancer treatment, and the defatted seed extract is used in the treatment of allergies.

COMMON NAME
Perilla

OTHER NAMES
Beefsteak plant, Chinese basil, purple perilla, wild sesame (English common names), Ban Tulsi (Bengali), Su Zi (Mandarin), Shosi, Egoma (Japanese). Different names are used for the different parts of the perilla plant used as foods or medicines.

BOTANICAL NAME/FAMILY
Perilla frutescens (L.) Britt.

There are several botanical variants that seem to be used interchangeably: *P. frutescens* var. *crispa*, *P. frutescens* var. *japonica* (family Lamiaceae or Labiatae [mint family]).

PLANT PARTS USED
Leaf, stem and the fruit (seed) are used.

CHEMICAL COMPONENTS

As different parts of the plant are used, this section will deal with each part individually.

Raw oil

Perilla seed contains 25–51% lipids. The raw perilla oil has been used as a drying oil in paints, varnishes, linoleum, printing ink and lacquers and for protective waterproof coatings on cloth. It has also been used for cooking and as a fuel.

Refined oil

The purified oil is rich in fatty acids including palmitic acid, linoleic acid, alpha-linolenic acid, stearic acid, eicosenoic acid and arachidic acid. The omega-3 essential fatty acid, alpha-linolenic acid, comprises over 60% of the oil (Tan et al 1998).

Defatted perilla seed extract

Defatted perilla seed extract is a concentrated ethanolic extract rich in polyphenolic compounds including rosmarinic acid and rosmarinic acid methyl ester and the flavones apigenin, luteolin and chrysoeriol. Normally, flavonoids exist as glycosides in plants; however, in perilla seed extract, they occur as aglycones (free flavonoids), which have more potent activity. The defatted extract is free of perillyl ketone, perillyl aldehyde and perillyl alcohol (Oryza Co 2003).

Leaf

The leaf contains flavones, including apigenin and luteolin; flavone glycosides, anthocyanins, phenolic compounds, including rosmarinic acid, and aldehydes including perillyl aldehyde (Makino et al 2003a).

Essential oil

The volatile oil is distilled from the dried foliage of perilla. It contains perillyl aldehyde, elsholtziaketone, perillyl ketone, citral and perillene, in addition to more than 70 other compounds (Ito et al 1999). Notably, rosmarinic acid is one of the major polyphenolic ingredients of perilla leaf. Perillyl aldehyde is used as a sweetener and flavouring agent. One of the aldehyde isomers is 2000-fold sweeter than sugar and 4–8-fold sweeter than saccharin. Perillyl alcohol, prepared from perillyl aldehyde, is used in fragrances (Misra & Husain 1987). There are different chemotypes of perilla; one genotype lacks perillyl aldehyde but has perillyl ketone (Brenner 1993).

MAIN ACTIONS

The herb has several different actions, and the part of the plant used will determine which is exhibited. As such, this review includes information about which part of the herb is responsible for the activity listed. Additionally, much research has been conducted with the rosmarinic acid and luteolin components isolated from perilla.

Anti-inflammatory action

Both the refined oil and seed extract demonstrate anti-inflammatory activity in vitro.

Refined oil

The pharmacological effects of the refined oil are associated with its high level of alpha-linolenic acid, which is metabolised in the body to eicosapentaenoic acid (EPA) and docosahexaenoic acid. EPA is a precursor of the series 3 prostaglandins, the series 5 leukotrienes and the series 3 thromboxanes, which have anti-inflammatory and anti-atherogenic properties. The effects have been shown clinically, as perilla seed oil significantly suppressed the generation of leukotrienes in patients with asthma in an observational study comparing two groups of patients with asthma, one of whom received perilla oil for 4 weeks. Ventilatory parameters, such as peak expiratory flow (PEF), forced vital capacity (FVC) and forced expiratory volume (FEV_1), increased significantly after 4 weeks' dietary supplementation in the treated group (Okamoto et al 2000). In vivo dietary perilla oil has been shown to alleviate inflammation in mice via decreasing the secretion of proinflammatory cytokines (Chang et al 2008).

Seed extract

Perilla seed extract, as well as its constituents luteolin, rosmarinic acid and chrysoeriol, has been shown to inhibit 5-lipoxygenase in vitro and therefore leukotriene synthesis. Leukotrienes are associated with both allergic and inflammatory disorders, including hay fever, asthma and inflammatory bowel disorders.

Anti-allergic activity

In both in vitro and animal models of allergy, perilla preparations have demonstrated anti-allergic effects. Luteolin and rosmarinic and caffeic acids are chiefly responsible for this activity.

Seed extract

The defatted seed extract has been shown to inhibit chemically induced type IV allergy and inflammation in vivo, with the luteolin constituent exhibiting the most potent activity.

Perilla seed extract has also been shown to inhibit histamine release from mast cells in a dose-dependent manner. The effect is more potent than for isolated flavonoids including catechin, quercetin and caffeic acid. Additionally, in a case report of perilla seed extract, 150 mg/day for 2 weeks selectively inhibited the production of serum IgE in two human subjects suffering allergic symptoms including sneezing, nasal obstruction and itchy eyes (Oryza Co 2003).

Leaf

Perilla leaf extract is thought to down-regulate Th2-type cytokine production and prevent the Th1/Th2 balance from shifting towards Th2-type immune responses. A study on the effects of perilla leaf extract on cytokine production in allergic reaction in mice found that it suppressed IgE and IgG antibodies as well as IL-4, IL-5 and IL-10 (Ishihara et al 1999).

An aqueous extract of perilla leaf was shown in vitro and in vivo to inhibit local and systemic

reactions in a mast cell-mediated immediate-type allergic reaction. Plasma histamine levels and cyclic adenosine monophosphate (AMP) were reduced in a dose-dependent manner. Perilla also inhibited IgE-induced tumour necrosis factor (TNF)-alpha production (Shin et al 2000). Oral administration of a hot water extract of perilla leaf was also shown to inhibit histamine release from mast cells and reduce scratching in an animal model of dermatitis (Wakame et al 2000).

Oral administration of a perilla leaf extract inhibited the inflammatory response in an induced allergic reaction in animals. Luteolin, rosmarinic and caffeic acids were isolated and identified as active constituents. Luteolin has been shown in vivo to inhibit TNF-alpha and arachidonic acid and reduce oedema (Ueda et al 2002). In another inflammatory model, perilla dose dependently reduced the allergic response in mice by over 40%. Rosmarinic acid was identified as the main active constituent (Makino et al 2001) and has been shown to decrease the inflammatory response and increase superoxide radical scavenging in vivo (Osakabe et al 2004a). An extract of perilla leaf with high levels of rosmarinic acid decreased cytokine activity in asthma-induced rats (Sanbongi et al 2004). A perilla leaf decoction was found to suppress IgA nephropathy in genetically predisposed rats, possibly through modulation of the intestinal mucosal immune system. Perilla suppressed proteinuria, proliferation of glomerular cells, serum levels of IgA, glomerular IgA and IgG depositions in the mice. Rosmarinic acid seems to produce this effect synergistically with other constituents (Makino et al 2003b).

Antioxidant activity

A methanolic extract of roasted defatted perilla seed has been shown to exert strong antioxidant activity, and upon fractionation, luteolin was identified as one of the active antioxidant constituents (Jung et al 2001). Rosmarinic acid inhibits NO and nitric oxide synthase (iNOS) in vitro (Qiao et al 2005, Renzulli et al 2004). Aqueous extract of perilla significantly inhibits free radical production by neutrophil leucocytes (Zekonis et al 2008).

Immunostimulant

Perilla leaf extract stimulates phagocytosis in vitro and in vivo (Simoniene et al 2005). An increase in neutrophil phagocytosis was noted after 7 days but was strongest after 4 weeks of treatment. A polysaccharide extract from perilla leaf has also demonstrated phagocytic ability both in vitro and in vivo (Kwon et al 2002).

Antimicrobial activity

Perilla may help prevent dental caries and periodontal disease. Perilla seed extract has been shown to have antimicrobial activity against oral cariogenic streptococci and periodontopathic *Porphyromonas gingivalis*. The luteolin constituent showed the strongest antimicrobial effect among the phenolic compounds tested (Yamamoto & Ogawa 2002).

Hepatoprotective effects

Perilla extract and its constituent rosmarinic acid have both been shown to be hepatoprotective against lipopolysaccharide-induced liver damage in mice, possibly due to the antioxidant activity (Osakabe et al 2002).

Hypocholesterolaemic effects

Hypocholesterolaemic effects of perilla have been demonstrated in vivo. Perilla oil lowers cholesterol by suppressing hepatic beta-hydroxy-beta-methylglutaryl-CoA (HMG-CoA) reductase activity (Du et al 2003). Perilla oil also lowers plasma triacylglycerol by suppressing fatty acid synthase (Kim et al 2004) and stimulating acyl-CoA oxidase (Kim & Choi 2005) in the liver.

Perilla oil mixed with borage and evening primrose oil has been shown to reduce cholesterol in older rats (Fukushima et al 2001).

Anticancer effects

Several constituents found in perilla have demonstrated anticancer effects in vitro and in experimental cancer models. This has prompted phase I and phase II clinical testing with one key active constituent, perillyl alcohol.

Conjugated alpha-linolenic acid from perilla oil has been shown to reduce the rate of carcinogenesis in a chemically induced rat mammary cancer model (Futakuchi et al 2002). The fibrinolytic and antioxidative activities of rosmarinic acid suppress the proliferation of mesangial cells in vivo (Makino et al 2002, Osakabe et al 2004b). Animal studies have demonstrated the ability of perillyl alcohol to inhibit tumorigenesis in the mammary gland (Yuri et al 2004) and skin (Lluria-Prevatt et al 2002). The precise mechanism of action is unclear, but it is thought that compounds other than the rosmarinic acid stimulate apoptosis (Lin et al 2007). Perillyl alcohol has been shown to inhibit part of the signal transduction cascade involved in uncontrolled cell proliferation, upregulate the mannose-6-phosphate receptor and induce apoptosis (Liston et al 2003, Xu et al 2004). Perillyl alcohol has also demonstrated an ability to decrease the release of vascular endothelial growth factor from cancer cells and encourage the expression of angiopoietin-2 by endothelial cells (Loutrari et al 2004). This indicates that perilla may play a role in decreasing the vascularisation of tumours and inducing regression. The effects of perillyl alcohol and its metabolite perillic acid on the proliferation of non-small cell lung cancer cells were investigated in vivo. Both elicited dose-dependent cytotoxicity, induced cell cycle arrest and apoptosis in a dose-dependent manner (Yeruva et al 2007).

Perillyl alcohol increases the sensitivity of cancer cells in vitro to radiation treatment of prostate cancer (Rajesh & Howard 2003), glioma (Rajesh et al 2003) and certain neck and head cancers (Samaila et al 2004).

Antidepressant activity

Several different constituents within perilla leaf have demonstrated effects on behaviour in vivo, most notably antidepressant effects. Perilla demonstrated

an antidepressant-like property in animal models of depression, possibly through cell proliferation in the hippocampus (Ito et al 2008b). Rosmarinic acid and caffeic acid have demonstrated antidepressant activity in a forced swimming test in mice. The activity is thought to be via some mechanism other than the inhibition of monoamine transporters and monoamine oxidase (Takeda et al 2002a). Apigenin from perilla significantly reduced immobility in a forced swimming test in mice, an effect mediated by dopaminergic mechanisms (Nakazawa et al 2003). Inhalation of L-perillaldehyde, a major component in the essential oil, shows antidepressant-like activity in mice through the olfactory nervous function (Ito et al 2008a).

Rosmarinic acid and caffeic acid have been shown to decrease the duration of the defensive freezing behaviour caused by fear and stress in animals (Takeda et al 2002b).

OTHER ACTIONS

Perilla oil has been shown to reduce the excessive growth of visceral adipose tissue in rats by down-regulating adipocyte differentiation in animals (Okuno et al 1997). This has direct relevance to obesity, as a high-fat diet not only accelerates the filling process of preexisting preadipocytes but also stimulates the proliferation of adipose precursor cells. Adipocyte differentiation, from adipoblasts to adipocytes, is a key factor underlying obesity.

A glycoprotein isolated from perilla oil has been shown to inhibit an early stage of HIV-1 replication without blocking viral adsorption in vitro (Kawahata et al 2002, Yamasaki et al 1998).

Perilla aldehyde has demonstrated vasodilatory activity in isolated rat aorta and appears to work by blocking Ca^{2+} channels (Takagi et al 2005). The clinical significance of this is currently unknown.

CLINICAL USE

The form most commonly used at the moment is the extract of defatted perilla seed; however, this review will also include information regarding other forms.

Cancer

Phase I clinical trials have shown a favourable toxicity profile, and preliminary data have indicated some chemotherapeutic efficacy in advanced cancers. In vitro studies suggest that perillyl alcohol inhibits the expression and function of androgen receptors in human prostate cancer cell line, suggesting that perillyl alcohol could be useful for intervention of prostate cancer (Chung et al 2006). Another in-vitro study of a combination of perillyl alcohol with a virally delivered therapeutic cytokine shows promise for both preventing and treating human pancreatic cancer without toxic effects (Lebedeva et al 2008).

However, perillyl alcohol (1200 mg/m^2 four times daily) failed to extend the time-to-progression in three phase II studies in patients with advanced ovarian carcinoma (Bailey et al 2002), prostate cancer (Liu et al 2003) and colorectal cancer. All trials were very small and had to contend with high dropout rates due to intolerability of the medicine. Despite encouraging preclinical results, perilla does not appear to zbe an effective treatment for advanced cancer.

Topical perillyl alcohol inhibits ultraviolet B-induced skin carcinogenesis in vivo so has been tested clinically for activity. A 1-month, double-blind, phase 1 trial of topically administered perillyl alcohol cream was trialled in 25 human subjects. They were monitored for toxicity and underwent histopathological evaluation. The topical cream was well tolerated. No serious cutaneous toxicities, systemic toxicities or histopathological abnormalities were observed. However, there was no significant difference between lesions appearing on the treated forearm versus the placebo-treated forearm (Stratton et al 2008).

Allergy

Based on traditional use, in vitro and in vivo studies and human trials, perilla leaf and defatted seed extracts are used for allergic respiratory disorders including hay fever, asthma and sinusitis. The refined oil may also help allergic and inflammatory respiratory conditions by regulating the arachidonic acid metabolism pathways and suppressing leukotriene generation.

A double-blind, randomised, placebo-controlled clinical trial showed a significant reduction in symptoms such as watery eyes, itchy eyes and itchy nose in 29 patients with seasonal allergic rhinoconjunctivitis, taking 50 or 200 mg of rosmarinic acid-enriched perilla for 21 days (Takano et al 2004). Responder rates were 55.6 and 70%, respectively. A drastic reduction in the number of neutrophils and eosinophils in nasal fluid was also demonstrated.

In an open clinical trial, 20 human subjects suffering allergic symptoms, including sneezing, nasal obstruction and itchy eyes and skin, were treated with 100–150 mg perilla seed extract daily (higher dose for persons over 60 kg) for 2 weeks. The subjects themselves evaluated changes in the severity of symptoms. Significant improvement was noted in 80% of the subjects for nasal obstructive symptoms, 40% reported a significant improvement in sneezing and half reported a significant reduction of itchy eyes (Oryza Co 2003).

A systematic review of double-blind randomised trials evaluating various herbal medicines in patients with allergic rhinitis concluded that perilla (part used not specified) showed promising results (Guo et al 2007).

Perilla leaf extract cream

Open studies of more than 100 children with atopic dermatitis found that perilla leaf extract cream improved symptoms in 80% of cases after 3 months' treatment (Yu & Kosuna 1997). Another open study with 20 allergic patients, using perilla leaf cream topically and perilla leaf extract orally, showed a general improvement in 90% of the patients after 2 months, with 30% reporting significant improvements (Yu et al 1997).

Dental caries and periodontal disease

Perilla seed extract inhibits the growth of cariogenic and inflammatory microorganisms including oral streptococci and *Porphyromonas gingivalis*

Clinical note — Perilla and traditional medicine systems

Perilla is an important ingredient of several Traditional Chinese Medicine (TCM) formulas. Perilla leaf is a key ingredient in Saiboku-to, a traditional Chinese formulation used in the treatment of type 1 hypersensitivity disorders including asthma (Nishiyori et al 1985). Saiboku-to contains *Bupleurum falcatum*, *Pinellia ternata*, *Poria cocos*, *Scutellaria baicalensis*, *Magnolia officinalis*, *Zizyphus spinosa*, *Panax ginseng*, *Glycyrrhizae uralensis*, *Zingiber officinale* and perilla. Another TCM formula containing perilla, Sam So Eum, is used to treat asthma and has been shown in an animal model to decrease airway hyperresponsiveness by restoring the immunomodulating cytokines. The anti-inflammatory effects of this formula are similar in effectiveness to prednisolone (Cho et al 2008). Perilla is also a component of the Banxia Houpu Decoction used for depression. It contains *Pinellia ternata*, *Poria cocos*, *Magnolia officinalis*, *Perilla frutescens and Zingiber officinale* (Luo et al 2000). Perilla leaf has been prescribed as one of the component herbs in certain Kampo (Japanese herbal) medicines that are used clinically for the improvement of depressive mood. These formulae demonstrate antidepressant-like effect in mice models through suppressing the hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis (Ito et al 2006).

(Yamamoto & Ogawa 2002). Perilla seed extract also reduces inflammation through inhibition of leucocyte production and radical scavenging activity. As such, application of the extract in the oral cavity is used to reduce dental caries and pericoronitis.

OTHER USES

Refined perilla oil is a good source of n-3 series alpha-linolenic acid.

DOSAGE RANGE

- Perilla leaf: extract equivalent to 4–9 g/day (Bensky & Gamble 1986).
- Refined perilla oil: 1000 mg capsules taken three to six times daily.
- Perilla seed extract (containing a minimum of 3.0% polyphenols): 100–150 mg/day (Oryza Co 2003).
- External use (dental caries and periodontal disease): 80–160 mg defatted perilla seed daily delivered directly into the oral cavity in the form of toothpaste, chewing gum or mouth rinse.

ADVERSE REACTIONS

Defatted perilla seed extract has very low toxicity. After administering 2000 mg/kg to mice for 2 weeks, no toxic effects were observed (LD_{50} for mice is therefore more than 2000 mg/kg). Dosage of 7.0 g/kg for 2 weeks did not produce any toxic effects in humans.

In Japan, 20–50% of long-term workers in the perilla industry develop dermatitis on their hands due to contact with perillyl aldehyde (Brenner 1993).

A 13-week subchronic oral toxicity study of perilla leaf extracts in drinking water did not show any acute toxicity. There were no treatment-related changes in body weight gain or in haematological or blood biochemistry values. Nor were there any treatment-related histopathological changes observed in the highest dose group (Yun et al 1999).

There has been a report of lipoid pneumonia in a 57-year-old man who had a history of ingesting green perilla oil, and there was also residual neurologic deficit of cerebral infarction with right hemiparesis (Kwang et al 1999).

Phase I and II clinical trials of perillyl alcohol for certain cancers have shown that gastrointestinal side effects and fatigue are the most common adverse reactions (Azzoli et al 2003, Bailey et al 2002, 2004, Liu et al 2003, Meadows et al 2002). Gastrointestinal effects are usually mild and include nausea, vomiting, bloating and belching. Doses were usually between 1200 and 1600 mg/m^2 four times daily.

The refined perilla oil is clear golden yellow. It is fully refined (neutralised, bleached and deodorised) and should be free of perillyl ketone, which is a potent lung toxin that causes increased microvascular permeability and pulmonary oedema in grazing animals (Waters et al 1993).

SIGNIFICANT INTERACTIONS

Controlled studies are not available, so interactions are based on evidence of activity and are largely theoretical and speculative.

Antihistamine agents

Theoretical additive effect is possible. Patients taking perilla concurrently with antihistaminic should be observed and drug doses modified if required.

Contraindications and precautions

None reported for perilla seed extract or refined oil; however, perilla leaf extract is contraindicated in diarrhoea (Bensky & Gamble 1986).

PRACTICE POINTS/PATIENT COUNSELLING

- Perilla exhibits anti-inflammatory, anti-allergic, antioxidant and anticariogenic activity. Preliminary evidence also suggests hepatoprotective and behavioural effects.
- Perilla leaf and defatted seed extracts are specifically used for allergic respiratory disorders including hay fever, asthma and sinusitis.
- Perilla leaf and defatted seed extract may down-regulate Th2-type cytokine production and prevent the Th1/Th2 balance from shifting towards Th2-type immune responses that may be associated with a range of allergic reactions and autoimmune disorders.
- Refined perilla oil is a good source of n-3 series alpha-linolenic acid, and extracts should be free of perillyl ketones and aldehydes.

PREGNANCY USE

Insufficient information is available to determine the safety of perilla during pregnancy.

PATIENTS' FAQs

What can this herb do for me?

Perilla is used in the treatment of allergic respiratory conditions, such as hay fever, asthma and sinusitis. Preliminary evidence suggests that it may be beneficial; however, more rigorous studies are still required to confirm effectiveness.

When will it start to work?

Relief of symptoms should be noticed within the first week, although it may take a couple of weeks to show a significant effect. For hay fever, it would be beneficial to start taking perilla at least 1 month before the onset of the hay fever season.

Are there any safety issues?

Perilla is very well tolerated and nontoxic. It can be used long term if indicated.

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Policosanol

BACKGROUND AND RELEVANT PHARMACOKINETICS

Policosanol is isolated from the waxes of plants such as sugar cane. The main component, octacosanol, has variable absorption from the small intestine and is chiefly metabolised by the liver and excreted in the faeces.

CHEMICAL COMPONENTS

Policosanol is a mixture of long-chain primary aliphatic alcohols (Arruzazabala et al 1993a). The alcohols have a chain length ranging from 24–34 carbons and the major components of the mixture are octacosanol (60–70%, w/w), triacosanol (10–15%, w/w) and hexacosanol (4–10%, w/w) (Francini-Pesenti et al in press). Octacosanol is regarded as the main active constituent.

MAIN ACTIONS

Lipid lowering

Cuban sugar cane policosanol (CSP), derived from the waxy coating of stems and leaves of sugar cane and other plant materials, has been shown to exert significant lipid lowering effects in animals and humans in numerous studies conducted by a single laboratory and using a CSP product manufactured by Dalmer laboratories (La Havana, Cuba). Tests investigating CSP with experimental models including rats, rabbits, dogs and monkeys have demonstrated reductions in circulating total cholesterol (TC) levels consistently greater than 13% (Kassis et al 2007). Similarly, human studies using CSP have shown significant reductions in total cholesterol and LDL-cholesterol.

Many of these previous findings must now be questioned because there has been a plethora of negative clinical and experimental studies published since 2006 which have been unable to detect lipid lowering activity for CSP and other policosanol preparations.

Reduces oxidation of LDL-cholesterol

This has been demonstrated in vitro at an equivalent dose of 5 and 10 mg/day (Menendez et al 2000).

Reduces platelet aggregation

This has been confirmed in animal models and randomised double-blind studies, with effects starting at 10 mg/day (Castano et al 1999a, Arruzazabala

et al 1993b, 2002). One clinical study found that a dose of 20 mg/day policosanol produces the same inhibitory effects on platelet aggregation as 100 mg aspirin daily (Arruzazabala et al 1997). A higher dose of 40 mg policosanol does not appear to produce any further antiplatelet effects according to another double-blind study (Arruzazabala et al 2002). Thromboxane, but not prostacyclin, generation induced by collagen is also inhibited by policosanol in clinical studies (Carbajal et al 1998a).

OTHER ACTIONS

Endothelial protection

Oral administration of policosanol to spontaneously hypertensive rats resulted in a significant reduction in circulating endothelial cells compared with controls. Moreover, comparison between groups revealed a lower frequency of aortic lesions in policosanol-treated animals than in untreated animals (Noa et al 1997).

Antihypertensive effects at very high doses

Tests in animal models have identified enhancement of propranolol-induced hypotensive effects with pretreatment at 200 mg/kg policosanol (Molina et al 1999), which is an extremely high dose and clinically irrelevant in humans.

Reduces atherosclerotic lesion development

According to one animal study, most policosanol-treated animals did not develop atherosclerotic lesions compared with an untreated group, and the thickness of fatty streaks that did develop with treatment had fewer foam cell layers than in controls (Arruzazabala et al 2000).

CLINICAL USE

Policosanol is most often used in the management of hyperlipidaemia and is sold as a lipid lowering agent in over 40 countries world-wide (Francini-Pesenti et al in press).

Hyperlipidaemia

Multiple clinical trials conducted with Cuban sugar cane policosanol (CSP), manufactured by Dalmer laboratories (La Havana, Cuba), support its use and indicate significant lipid lowering activity. Studies conducted by other research groups outside Cuba have not been able to reproduce the results obtained in the original studies, casting doubt over the product's lipid lowering activity. This review will therefore include information from all research parties, allowing the readers to make their own judgment as to whether policosanol is an effective treatment for hyperlipidemia.

Numerous randomised, double-blind clinical trials conducted prior to 2006 demonstrated significant cholesterol-lowering effects of oral policosanol (Castano et al 2001b, Mas et al 1999, Menendez et al 2000, Pons et al 1994, Torres et al 1995). Several previous studies conducted with postmenopausal women have confirmed efficacy in this population (Castano et al 2000, Mas et al 1999, Menendez et al 2000, Mirkin et al 2001, Pons et al 1994, Torres et al 1995). Overall, these results show that a daily dose of 5 mg policosanol may:

- reduce LDL-cholesterol by 11–18%
- reduce total cholesterol by 8–15%
- increase HDL by 8–15%,

whereas a higher dose of 20 mg policosanol daily can:

- reduce LDL-cholesterol by 31%
- reduce total cholesterol by 23%
- increase HDL by 27%.

Recent controversy

It is important to note that previous studies had used the same specific policosanol product and research had been conducted almost entirely by the same research group in Cuba and involved Hispanic patients. In 2006 the evidence base shifted dramatically because five negative clinical studies were published which were conducted by different research teams around the world, using either Cuban or non-Cuban policosanol products.

In Germany, Berthold et al conducted a 12-week randomised study of 143 Caucasian subjects with hypercholesterolaemia or combined hyperlipidaemia. The multi-centre study used CSP at doses of 10, 20, 40 and 80 mg/day. In contrast to previous studies, policosanol failed to significantly reduce LDL-cholesterol, total cholesterol, HDL-cholesterol, triglycerides and other lipid parameters at all test doses (Berthold et al 2006). In a US double-blind, placebo controlled trial of 40 healthy adults with mild hypercholesterolaemia, conducted by Dulin et al (2006), subjects were assigned to receive oral policosanol 20 mg or placebo once daily for 8 weeks. No significant changes were seen for LDL-cholesterol, total cholesterol, HDL-cholesterol, triacylglycerol, C-reactive protein and nuclear magnetic resonance spectroscopy-determined profiles. Also in the US, Cubeddu et al (2006) divided subjects with LDL-cholesterol (LDL-C) levels from 140 to 189 mg/dL into four groups and compared policosanol 20 mg to atorvastatin 10 mg, combination therapy or placebo for 12 weeks (Cubeddu et al 2006). In total, 99 patients took part and groups were well matched at baseline. Yet again, policosanol failed to have a significant effect on any lipid parameter and produced no additional lipid lowering effects when added to atorvastatin. In Canada, Kassis & Jones (2006) compared policosanol 10 mg/day to placebo in 21 people over a period of 28 days. The double-blind, crossover study also failed to find significant changes to plasma lipid levels for total, LDL-C, HDL-C and triacylglycerol concentrations with policosanol treatment. In South Africa, Greyling et al (2006) conducted a double-blind study involving 19 hypercholesterolaemic and familial hypercholesterolaemic subjects who received either policosanol 20 mg/day or placebo for 12 weeks. After a 4-week wash-out period, the interventions were crossed over and treatment recommenced. No significant differences in total cholesterol and LDL-C from baseline to end or between policosanol and placebo

Clinical note — Policosanol controversy

It is currently uncertain whether policosanol has significant lipid lowering activity due to the recent spate of negative clinical trials which have failed to confirm earlier positive results. Several theories may explain the discrepancy such as differences in the purity and composition of different policosanol products, insufficient test time-frames, differences between test subjects and, of course, researcher bias.

Researchers external to the original Cuban research groups have begun testing these different theories to uncover the answer. Theories proposing differences in octacosanol content have been discounted as the various policosanol products tested externally have contained similar concentrations to the original Cuban blend. Another suggestion is that products may have differed in minor alcohol content, explaining the disparate results. To test this theory, Cuban policosanol has been directly compared to other policosanol products in various animal models. Using a hamster model, Kassis et al compared Dalmer Cuban policosanol to an alternative Degussa policosanol mixture and found that neither treatment had a significant effect on lipids (Kassis et al 2007). A second research team headed by Marinangeli also compared Cuban policosanol to another product with a similar amount of octacosanol and found no differences between them for tissue, plasma and faecal policosanol levels in an animal model (Marinangeli et al 2007). In regards to time frames, Cuban clinical studies indicate that lipid lowering activity can be observed by 4 weeks of treatment and reaches a maximal effect between 6 and 8 weeks. Studies conducted by Berthold et al (2006), Greyling et al (2006) and Cubeddu et al (2006) lasted 12 weeks and still found no significant activity so this theory can also be discounted. Finally, genetic differences between test subjects and differences in dietary habits could account for the varied responses between test subjects, however this appears unlikely.

were seen in the hypercholesterolaemic or familial hypercholesterolaemic groups.

Since 2006, the negative evidence has continued to accumulate as studies using animal models and clinical trials consistently fail to find significant lipid lowering activity for either CSP or its other forms (Francini-Pesenti et al in press, Kassis et al 2007, Marinangeli et al 2007, Kassis 2008, Kassis & Jones 2008).

Studies of type 2 diabetes

Studies conducted prior to 2006 indicate that policosanol has proven effects in dyslipidaemia secondary to type 2 diabetes mellitus (Crespo et al 1999, Torres et al 1995). Until these results can be confirmed by other research groups, these results remain uncertain.

Comparative trials with HMG-CoA reductase inhibitor

Whilst several randomised, double-blind studies comparing the effects of policosanol with standard hyperlipidaemic treatment (with statin drugs such as simvastatin and pravastatin) have produced favourable results (Alcocer et al 1999, Castano et al 1999b, Crespo et al 1999, Prat et al 1999, Torres et al 1995, Castano et al 2003b) it now appears unlikely that policosanol has lipid lowering effects comparable to statin drugs.

Concurrent use with omega-3 essential fatty acids

Due to the favourable effects of omega-3 fatty acids (FAs) in cardiovascular disease, in practice clinicians have recommended policosanol together with fish-oil supplements. According to an 8-week, double-blind, randomised study, the combination effectively reduced total cholesterol, LDL-C and triglycerides and increased HDL-C (Castano et al 2005). The study of 90 patients with type II hypercholesterolaemia found that when omega-3 FAs (2 g/day) were combined with policosanol (10 mg/day), there was a significant decrease in total cholesterol (15.3%) and triglycerides (14.7%), and a significant increase in HDL-C (15.5%). These results require substantiation by other research groups before they can be confirmed.

Concurrent use with beta-blockers

A 3-year randomised study of 205 older hypercholesterolaemic patients taking beta-blockers to showed that after 1 year of therapy, policosanol significantly reduced LDL-C (20.9%), total cholesterol (19.3%) and triglycerides (25.7%) and increased HDL-C levels (4.1%), effects that lasted for the duration of the study (Castano et al 2004a). The frequency of mild, moderate or severe adverse events was lower in the policosanol group than in the placebo group; however, an additional reduction in SBP and DBP was observed in the policosanol patients compared with those in the placebo group. Until these results can be confirmed by other research groups, these results remain uncertain.

Wheat-germ-derived policosanol

No beneficial effects on blood lipid profiles were observed in a double-blind, randomised study of 58 subjects with normal to mildly elevated plasma cholesterol who were given 20 mg wheat-germ policosanol in a short 4-week study (Lin et al 2004).

Intermittent claudication

Policosanol treatment for intermittent claudication has produced encouraging results in several randomised studies (Castano et al 1999b, 2001a, 2003a). Policosanol 10 mg/day taken for 6 months significantly increased initial claudication distance by approximately 70 metres and absolute claudication by approximately 140 metres in one double-blind study, whereas placebo produced no changes (Castano et al 1999b). A single-blind study using 20 mg policosanol daily showed significant improvements

after 6 months' treatment, which further increased after 12 months (Castano et al 2001b). In both studies patients in the policosanol group reported improvements in lower limb symptoms that were greater than those in the placebo group.

More recently, policosanol (10 mg twice daily) was shown to be as effective as ticlopidine (250 mg twice daily) for improving walking distances of claudicant patients (Castano et al 2004b). In the 20-week double-blind, randomised study of 28 subjects, policosanol significantly increased mean values of initial and absolute claudication distances from 162.1 to 273.2 metres and from 255.8 to 401.0 metres, respectively, which was not significantly different to ticlopidine. Both treatments were well tolerated.

In 2008, a randomised, double-blind study comparing policosanol (10 mg/day) to aspirin (100 mg/day) was published showing that policosanol modestly but significantly increased the initial and absolute claudication walking distances whereas no change occurred with aspirin (Illnait et al 2008). The study involved 39 volunteers and treatment lasted for 10 weeks.

Until these results can be confirmed by other research groups, these results remain uncertain.

OTHER USES

Preexisting coronary heart disease (CHD)

A randomised double-blind study of 45 subjects with documented CHD found that a dose of 10 mg policosanol daily increased maximum oxygen uptake and exercise ECG responses. The effects were further enhanced by co-administration of 125 mg aspirin (Stusser et al 1998).

Cerebrovascular disease

In two different experimental models policosanol had anti-ischaemic activity when administered after induction of cerebral ischaemia, suggesting a possible therapeutic effect in CVD (Molina et al 1999).

DOSAGE RANGE

The doses tested in clinical trials range from 5–20 mg/day.

More specific doses

- Hypercholesterolaemia: 5–20 mg/day (uncertain efficacy).
- Intermittent claudication: 10–20 mg/day — 3 months' continual use may be required before effects are observed.
- Platelet inhibition: 10 mg/day.

Policosanol is usually taken after the evening meal.

TOXICITY

Studies using several animal models have confirmed no carcinogenic effects and no signs of toxicity at doses as high as 500 mg/kg (Aleman et al 1994a, 1994b). This dose is hundreds of times greater than the maximal recommended therapeutic dose (20 mg/day), thereby indicating an excellent safety profile (Mesa et al 1994).

ADVERSE REACTIONS

A pharmacovigilance study of 2252 subjects aged 60 or more years with coronary, cerebrovascular and peripheral artery disease and treated with policosanol (5, 10 or 20 mg/day) at seven major medical centres found that long-term tolerability of policosanol in elderly patients at high vascular risk was very good (Fernandez et al 2004).

SIGNIFICANT INTERACTIONS

Aspirin

Increased antiplatelet effects may develop — patients taking aspirin and policosanol concurrently should be observed for increased bleeding or bruising.

Warfarin

Current evidence suggests that there is no interaction between policosanol and warfarin. One clinical study confirmed that the addition of policosanol to warfarin therapy does not enhance the prolongation of the bleeding time induced by warfarin alone (Carbajal et al 1998b). Caution with doses > 10 mg/day.

CONTRAINDICATIONS AND PRECAUTIONS

Suspend use of high doses 1 week before major surgery.

PREGNANCY USE

Safety has been investigated in animal tests with no evidence of teratogenicity or any other embryonal toxicity (Rodriguez & Garcia 1994, 1998, Rodriguez et al 1997).

PATIENTS' FAQs

What can this supplement do for me?

It is uncertain whether policosanol can significantly lower cholesterol levels. Early studies suggested this effect is as strong as conventional cholesterol-lowering medications however more recent studies have found no effect. It also has some blood-thinning activity, may be effective in intermittent claudication and can increase total walking distance.

When will it start to work?

Early studies suggest maximal lipid lowering effects are seen after 6-8 weeks of continuous use however new evidence casts doubt over its efficacy.

Are there any safety issues?

Policosanol has a wide safety margin and is well tolerated.

PRACTICE POINTS/PATIENT COUNSELLING

- It is uncertain whether policosanol can still be considered an efficacious lipid-lowering treatment because of a recent spate of negative studies showing no significant effect.
- It is a potentially useful treatment in claudication however more research is required to confirm its effects.
- Policosanol has significant platelet aggregation inhibitor activity.
- Safety studies indicate that it is well tolerated and has a wide safety margin.

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Prebiotics

HISTORICAL NOTE Gibson & Roberfroid (1995) introduced the concept of prebiotic as 'a non-digestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon and thus improves health'. This concept has been further developed to define prebiotics as 'selectively fermented ingredients that allow specific changes, both in the composition and/or activity of the gastrointestinal microflora that confers benefits upon host wellbeing and health'.

BACKGROUND AND RELEVANT PHARMACOKINETICS

Numerous components appear to have prebiotic characteristics, but some will not be classified as prebiotics because they may not meet all the criteria i.e. not metabolised (hydrolysed or absorbed) in the upper gastrointestinal tract, demonstrates selective fermentation by one or a limited number of potentially beneficial intestinal bacteria, and change the colonic microflora to a healthier composition (Gibson & Roberfroid 1995, Roberfroid 2007). To date, the most well-known prebiotics are inulin, lactulose, fructo-oligosaccharides (FOS) and galacto-oligosaccharides (GOS) (Roberfroid 2007).

One of the key characteristics of prebiotics is to stimulate the selective growth of intestinal microorganisms and, in particular, the growth of lactobacilli and bifidobacteria.

Studies have demonstrated that the intestinal microflora of breastfed infants is characterised by high levels of bifidobacteria and lactic acid bacteria because oligosaccharides occur naturally in breast milk. Formula-fed infants were found to have more bacteroides, clostridia and enterobacteriaceae and lower levels of the beneficial microorganisms (Coppa et al 2006).

Bifidobacteria are well-known defences against pathogenic bacteria and are significant for promoting gut health (Cummings & Macfarlane 2002, Brunser et al 2006, Gibson 1998, Gibson & Roberfroid 1995). In addition to stabilising the gut microflora, prebiotics may have a role in allergy; reports indicate that infants with allergy had lower levels of lactobacilli and bifidobacteria (Bjorksten et al 2001) and feeding prebiotics was able to rectify this. Increasingly, prebiotics have been added to infant milk formulas in order to simulate the composition of human breast milk prebiotic oligosaccharides.

In recent years, there has been a focus on using multiple prebiotics together rather than a single component; combinations of long-chain FOS and short-chain GOS have been utilised mainly because different gastrointestinal microorganisms may require different substrates for optimal growth.

In both adults and the young, prebiotics are reported to have other health-promoting properties and they may have a role in the management of a number of diseases and conditions. Altered gastrointestinal microflora and abnormal colonic fermentation is also noted in some conditions such as inflammatory bowel disease (IBD) and irritable bowel syndrome (IBS) (King et al 1998); treatment with prebiotics or synbiotics may normalise the altered microflora.

Prebiotics as indigestible components are known to have laxative properties and are used as bulking agents for gastrointestinal health; the end products of the prebiotic fermentation in the colon are short-chain fatty acids (SCFAs), which have direct effects on the intestinal cells and stimulate intestinal peristalsis (Gibson 1999, 1998, Gibson & Roberfroid 1995, Gibson et al 1995).

Both lactobacilli and bifidobacteria species in the colon have important roles in immune stimulation and prevention of infection and diarrhoea (Gorbach et al 1987, Macfarlane et al 2006, Saavedra et al 1994). Some bifidobacteria and lactobacillus species may have antimutagenic and antitumour properties; prebiotics such as inulin appear to inhibit colonic cancer cell growth (Pool-Zobel & Sauer 2007).

The anti-inflammatory characteristics do not extend to all prebiotics, as some prebiotics have been reported to have adverse effects; in particular, intake of FOS has been reported to promote bacterial translocation and increase mucosal irritation in some animal studies (Bovee-Oudenhoven et al 2003).

CHEMICAL COMPONENTS

Prebiotics are principally oligosaccharides of which there are various types: oligofructose, inulins, isomalto-oligosaccharides, lactosucrose, lactulose, pyrodextrins, xylo-oligosaccharides.

Inulins are multiple fructose units and inulin degradation results in oligofructose. Oligosaccharides occur naturally in breast milk. Fructans are linear or branched fructose polymers and the GOS are synthesised from lactose by the action of beta-galactosidase. FOS are the inulin-type fructans

Clinical note — The hygiene hypothesis

The intestinal microflora is crucial for the development of the immune system (Ouwehand et al 2002) and the 'hygiene theory' suggests that exposure to microorganisms is required for this. The consumption of foods containing microorganisms for health-promoting properties has a long history. Probiotics are microorganisms that can 'beneficially affect the host physiology by modulating mucosal and systemic immunity, as well as improving nutritional and microbial balance of the intestinal tract' (Gibson & Roberfroid 1995, Salminen et al 1998).

Clinical note — Synbiotics
Synbiotics are a combination of both prebiotic(s) and probiotic(s); the selection of both of these constituents is based on the premise that they will work in synergy (Bengmark 2005). A combination of *Lactobacillus paracasei* and FOS results in increased lactobacillus and bifidobacteria and decreased clostridium and enterobacterium. In recent years, there has been a trend to increasingly use synbiotics for a synergistic health promoting effect, but this also makes it difficult to evaluate the individual effects of each component.

that can be readily obtained from plant sources. Both GOS and FOS are widely used in the food industry (Yang & Silva 1995).

FOOD SOURCES

Low levels of prebiotics can be found in artichoke, asparagus, bananas, chicory, garlic, leek, onions and wheat. Inulin and oligofructose occur naturally in food. Commercially produced prebiotics are extracted from chicory roots or synthesised from sucrose and are used widely in the food industry. Dietary intake of prebiotics is variable, with the intake for Americans being in the range 1–4 g/day and on average a higher intake among Europeans who consume 3–10 g/day (Delzenne 2003).

DEFICIENCY SIGNS AND SYMPTOMS

Clear deficiency signs are difficult to establish because the symptoms may vary enormously. Local signs and symptoms of disruption of the intestinal microflora leading to an imbalance (intestinal dysbiosis) include bloating, flatulence, abdominal pain, diarrhoea and/or constipation and fungal overgrowth (such as *Candida*). An imbalance of gastrointestinal microflora can be caused by the use of antibiotics, and chronic diarrhoea or constipation. Administration of prebiotics, probiotics or synbiotics is used as a means of restoring this microflora imbalance.

MAIN ACTIONS

In recent years, there has been a focus on the utility of prebiotics, but at present the exact mechanisms of their action remain unclear although there are a number of proposals.

Stimulation of beneficial bacteria

Many animal and human studies have demonstrated that prebiotics modulate the gut microflora by increasing bifidobacteria and lactobacilli levels (Bouhnik et al 1997, Gibson & Wang 1994, Langlands et al 2004).

Prebiotics are fermented by microflora in the proximal colon resulting in the production of short-chain fatty acids (acetic, propionic and butyrate acids) and gas (CO_2 and H_2). Consequently, the lower intraluminal pH inhibits the growth of *Bacteroides* spp and increases Lactobacilli and Bifidobacteria (Walker et al 2005). As a result of prebiotics stimulating the growth of beneficial bacteria, these microorganisms secrete antimicrobial compounds and can inhibit colonisation of the pathogenic bacteria and prevent their adherence to the intestinal epithelium (Shoaf-Sweeney & Hutkins 2009). The adherence can be also limited as a result of the oligosaccharide's terminal sugars interfering with the receptors on the pathogenic bacteria (Hopkins & Macfarlane 2003, Zopf & Roth 1996); reduced adherence of enteropathogenic *E. coli* in HeP and $CaCO_2$ cells has been noted with GOS (Shoaf et al 2006).

Immunomodulation

The mechanisms whereby prebiotics have immunomodulatory effects (modulate cytokine and antibody production) are largely unknown and the proposed mechanisms include beneficial changes in the intestinal microflora, increased production of both mucin and short-chain fatty acids (SCFAs). There may also be changes in the gut-associated lymphoid tissues (GALT) as a result of prebiotic fermentation in the colon (Forchielli & Walker 2005). The SCFAs are beneficial to the host as an energy source and enhance mucosal integrity with increased production of mucin, binding to receptors on immune cells within gut lymphoid-associated tissue (GALT) and limiting translocation; mucin may limit bacterial translocation. There is little information about the effects of prebiotics on mucin production but an animal study noted increased mucin production associated with inulin treatment (Fontaine et al 1996).

Both prebiotics and probiotics are reported to have beneficial effects in reducing the effects of colitis by altering the gastrointestinal microflora due to stimulating growth of the protective bacteria and reducing colonisation with potentially hazardous bacteria (Sartor 2004). Prebiotics (mainly inulin and FOS) may also ameliorate inflammation as a result of reducing the activity of proinflammatory transcription factors (e.g. NF-κB), and by the increased production of SCFAs (Cavin et al 2005, Holma et al 2002, Kinoshita et al 2002, Millard et al 2002). Animal studies show conflicting findings with some reporting less inflammation (Cherbut et al 2003) and others have reported that there is no protection from FOS in rat models of colitis (Moreau et al 2003). In recent years, some human studies have been undertaken and mixed results are reported. Butyrate is a major source of energy for colonocytes, and in vitro studies indicate that butyrate has anti-inflammatory effects (Saemann et al 2000, Segain et al 2000); butyrate and acetate enhance mucin secretion.

Cancer prevention

Various in vitro and animal studies have been conducted to investigate the role of prebiotics and synbiotics for their anticancer effects, but there are only a limited number of studies in humans (Pool-Zobel & Sauer 2007). Animal studies have shown that prebiotic treatment is beneficial in reducing precancerous aberrant crypt foci and the effects

are more pronounced with synbiotics. Rowland et al (1998) reported that the effect is enhanced with synbiotics such as inulin + *B. longum* in their study of azoxymethane-induced aberrant crypt foci in rats. Oligofructose-enriched inulin plus *Lactobacillus rhamnosus* and *Bifidobacterium lactis* treatment prevented azoxymethane-induced suppression of natural killer (NK) cell activity in Peyer's patches (Roller et al 2004) and similarly a study (Le Leu et al 2005) demonstrated increased apoptotic response with resistant starch + *B. lactis* treatment.

OTHER ACTIONS

Mineral metabolism

Animal studies have indicated that prebiotics such as inulin and oligofructose can affect calcium bioavailabilty and increase calcium absorption. A number of mechanisms have been proposed for this action, including the increased production of SCFAs, which increase the solubility of minerals and also facilitates the colonic absorption of calcium and magnesium (Demigne et al 2008). Human studies have mostly investigated small numbers of participants and have produced mixed findings (Scholz-Ahrens et al 2007).

CLINICAL USE

Irritable bowel syndrome (IBS)

A multicentre, prospective, randomised, double-blind, placebo-controlled study by Olesen & Gudmand-Hoyer (2000) did not find benefits for the use of FOS in the treatment of IBS, similar to the findings of Hunter et al (1999) who utilised oligofructose in their double crossover study investigating IBS. In contrast, a study with a dietary mixture containing a number of components, including inulin plus *Lactobacillius acidophilus*, *Lactobacillius sporogenes* and *Streptococcus thermophilius* was given to one group of patients with IBS (n = 37) over a 5–7 month period and the control group (n = 28) received usual care; the supplement treatment resulted in significant improvements in abdominal pain, distension and constipation (Astengiano et al 2006).

Inflammatory bowel disease (IBD)

In a study of patients with active IBD, 14 patients presenting ulcerative colitis (UC) and 17 patients presenting Crohn's disease (CD) received either standard medication treatment or the medications with an additional 10 g/day lactulose dose for 4 months; at the end of the study there were no differences in the clinical or endoscopic score, although the UC group receiving the lactulose treatment reported an improved quality of life compared to the control group (P = 0.04) (Hafer et al 2007).

Crohn's disease (CD)

At present, the role of prebiotics in the management of CD remains unknown due to a limited number of studies.

A small open-label study of 10 patients with active ileo-colonic Crohn's disease, who were treated with a combination of prebiotics (15 g/day FOS) reported a significant reduction in disease activity scores and inflammation with an increase in IL-10-positive dendritic cells and toll-like receptor 2 and toll-like receptor 4 expression; it is noteworthy that patients entering remission had increased mucosal-associated bifidobacteria (Lindsay et al 2006).

However, a randomised controlled trial of 30 patients with CD postoperative ileocaecal resection, who were treated with Synbiotic 2000, a combination of four prebiotic components + probiotic mixture of four lactic acid strains (*Pediacoccus pentoseceus*, *Lactobacillus raffinolactis*, *Lactobacillus paracasei susp paracasei* 19, *Lactobacillus plantarum*, 2.5 g beta-glucans, 2.5 g inulin, 2.5 g pectin, 2.5 g resistant starch), did not show prevention of relapse 24 months later (Chermesh et al 2007). In another study (duration: 13.0 ± 4.5 months) (Fujimori et al 2007), 10 non-hospitalised patients with active CD were treated with high-dose symbiotic therapy consisting of bifidobacterium and lactobacillus (75 billion colony-forming units (CFU)/day) + psyllium (9.9 g/day); only three patients did not experience any benefit.

These differing results may be due to small sample size in the studies.

Ulcerative colitis (UC)

Information from a number of animal studies has indicated that prebiotics may be of therapeutic value in UC and human studies, which appear to show similar results. A small placebo-controlled study of 19 patients with active UC (mild/moderate) received prebiotic treatment (oligofructose-enriched inulin, ratio 1:1) plus 3 g/day of mesalazine for 2 weeks indicated less abdominal pain and a reduction of intestinal inflammation as determined by calprotectin levels which decreased after a week of treatment but there was no change in prostaglandin E2 (PGE2) secretion and interleukin (IL)-8 production (Casellas et al 2007).

In a double-blind, randomised controlled pilot study of 18 patients with active UC, synbiotic treatment with 12 g oligofructose-enriched inulin (1:1) plus *Bifidobacterium longum* for 4 weeks resulted in reduced colonic inflammation, decreased human beta-defensin mRNA, tumour necrosis factor-alpha (TNF-alpha) and IL-1alpha, and improved sigmoidoscopy scores, although there was no difference in clinical measures (Furrie et al 2005).

In a randomised, controlled study by Fujimori et al (2009), the efficacy of synbiotic therapy compared to either prebiotics or probiotics was conducted in 120 outpatients with UC in remission. Each group of patients enrolled in the study was treated with either ingesting one capsule per day consisting of *B. longum* 2×10^9 colony-forming units (probiotic group), or 2 × 4 g doses of psyllium (prebiotic group) or being treated with both the probiotic + prebiotic (synbiotic group) for 4 weeks. At the end of the study, C-reactive protein decreased significantly (P = 0.04) and the quality

of life scores in the Inflammatory Bowel Disease Questionnaires (IBDQs) were also significantly improved for the symbiotic treated group; the score for bowel function was significant in the prebiotic group ($P = 0.04$).

Pouchitis

There are only a limited number of studies that have investigated the role of prebiotics or synbotics in pouchitis.

A small open-label study of 10 patients with pouchitis (antibiotic-refractory or antibiotic-dependent), treated with a symbiotic mixture of FOS + *Lactobacillus rhamnosus* GG (LGG), reported complete remission as determined by clinical and endoscopic criteria (Friedman & George 2000). In a crossover study of 20 patients with ileal pouch–anal anastomosis, daily treatment with 24 g of inulin or placebo for 3 weeks did not change the clinical activity scores although there was a reduction in inflammation ($P = 0.01$), and increased faecal butyrate concentrations; lactobacilli and bifidobacteria levels were not affected although a significant reduction in faecal levels of *Bacteroides fragilis* was reported (Welters et al 2002).

Constipation

The use of lactulose has a long history and it has been used successfully to treat constipation (de Schryver et al 2005, Petticrew et al 1997). Likewise, FOS and GOS also have laxative effects; Gibson et al (1995) demonstrated that feeding 15 g of FOS or 15 g inulin per day could significantly increase stool output.

Diarrhoea

Various prebiotic components have been utilised in clinical trials to evaluate their efficacy in diarrhoea of different origins.

Traveller's diarrhoea

A double-blind, randomised controlled study of 244 people travelling to medium–high risk destinations and at risk of traveller's diarrhoea reported that those subjects who were treated with FOS (10 g) experienced increased wellbeing and less severe diarrhoea although there was no significant difference in the incidence of diarrhoea (Cummings et al 2001).

Clostridium difficile-associated diarrhoea (CDAD)

In a randomised, controlled, double-blind study, 142 patients with CDAD in hospital were randomised to receive oligofructose or placebo as well as the standard antibiotic treatment for 30 days and followed up 30 days later; the prebiotic-treated patients had increased bifidobacteria levels, reduction in the rate of relapse and experienced significantly less diarrhoea (8% vs 34% in the placebo group, $P < 0.001$) (Lewis et al 2005a).

In another randomised controlled double-blind study of 435 patients in hospital, who were receiving all antibiotics, patients were randomised to receive oligofructose for 7 days or a placebo, with follow-up for another 7 days, there was a significant increase in bifidobacteria concentrations in the prebiotic group although there was no difference in the incidence of *Clostridium difficile* (Lewis et al 2005b).

Allergic disease and food hypersensitivity

A Cochrane systematic review (Osborn & Sinn 2007) investigated the effectiveness of prebiotics for the prevention of allergic disease or food hypersensitivity in infants; of the seven studies that were assessed, there were only two ($n = 432$) that reported an allergic disease outcome; meta-analysis determined no significant difference in eczema. The study authors noted the marked heterogeneity with regard to the study populations, measures of eczema and also the prebiotics used. Moro et al (2006) reported that FOS + GOS combination reduced the development of atopic dermatitis in their study of infants at high risk from atopy. In contrast, Ziegler et al (2007) did not select infants based on their allergy risk and found no significant difference in eczema.

In a prospective, randomised, double-blind, placebo-controlled study of 134 infants, Arslanoglu et al (2008) reported that healthy infants of parents with a history of atopy, fed a hypoallergenic prebiotic-supplemented formula containing a mixture (8 g/L) of neutral short-chain GOS and long-chain FOS ($n = 66$ intervention group; $n = 68$ placebo group), during the first 6 months of life had fewer infections and allergic symptoms at follow-up. In another study by the same team, infants fed milk formula plus 8 g/L GOS/FOS for 6 months resulted in beneficial antibody profile (van Hoffen et al 2009).

Cancer

A randomised, double-blind, placebo-controlled study investigated the effects of a symbiotic mixture on immune modulation in patients with colon cancer ($n = 34$) post 'curative resection' and polypectomised patients ($n = 40$); the symbiotic treated group received encapsulated *Lactobacillus rhamnosus* GG (LGG) 1×10^{10} CFU + *Bifidobacterium lactis* Bb12 (Bb12) 1×10^{10} CFU + 10 g of inulin enriched with oligofructose on a daily basis for 12 weeks; overall both groups receiving the symbiotic treatment demonstrated minor effects on some of the immune markers (Roller et al 2007). Likewise in another randomised, double-blind, placebo-controlled study of 80 patients (37 colon cancer and 43 polypectomised) by this group, a number of colorectal cancer biomarkers were positively affected by 12 weeks' symbiotic treatment (Rafter et al 2007).

Bone health

A double-blind, randomised, crossover study with a 9-day intervention period and 19 days washout period investigating calcium absorption in 12 menopausal women reported an increased calcium absorption ($P = 0.04$) in women taking the yoghurt drink (2 × 200 mL/day) rich in transgalactooligosaccharides (20 g/day) (van den Heuvel et al 2000).

Griffin et al (2002) conducted a large, randomised, crossover study of 59 young girls to investigate the effect of either inulin or inulin + oligofructose (8 g/day) for 3 weeks with a 2-week washout period, in addition, all participants took 1500 mg/day calcium (2 glasses calcium-fortified orange juice); at the end of the study, the inulin + oligofructose-treated group was reported to have significantly higher calcium absorption. Studies by Abrams et al (2005) have supported these findings.

OTHER USES

Liver disease — hepatic encephalopathy

Lactulose has been used routinely as part of the treatment for hepatic encephalopathy although the exact mechanism of its action is still undetermined; lactulose treatment results in normalising of the intestinal microflora, lowering faecal pH and increasing nitrogen excretion (Ballongue et al 1997, Elkington et al 1969).

Pancreatitis

Some studies have found that symbiotic supplementation was more beneficial than prebiotics alone for improved systemic inflammatory response in patients with acute pancreatitis (Olah et al 2005).

DOSAGE RANGE

Prebiotics are known to induce unfavourable side effects such as abdominal pain, bloating, borborygmi and excessive flatulence when used in high doses; these symptoms may diminish over time or with dose reduction. However, the initial doses should be small and increased gradually dependent on gastrointestinal tolerance. GOS: 8–15 g/day; higher doses may lead to undesirable gastrointestinal symptoms such as cramping, abdominal pain and diarrhoea. FOS: 10–15 g/day; some report adverse side effects at 14 g, whereas 10 g is better tolerated.

TOXICITY

Overall, prebiotics have a good profile but their consumption can result in some adverse side effects. (See ADVERSE REACTIONS below.)

ADVERSE REACTIONS

There are many reports of transient gastrointestinal side effects of prebiotic treatment; symptoms such as abdominal pain, bloating, diarrhoea and flatulence are commonly reported. The severity of the symptoms is dose dependent. The more troubling aspect of prebiotics is their potential for enhancing bacterial translocation, although the findings are mixed.

Studies in rats have shown that both inulin and FOS not only increased intestinal lactobacilli and bifidobacteria colonisation, but also enhanced translocation of *Salmonella enterica serovar Enteritidis* and the caecal contents also contained *Salmonella* although calcium administration was noted to resolve this problem (Bovee-Oudenhoven et al 2003, Ten Bruggencate et al 2004). Reduced bacterial translocation to the liver has been reported in rats with Dextran Sulphate Sodium (DSS)-induced colitis when fed oligofructose, whereas feeding multiple components such as oligofructose, inulin, and *Bifidobacterium infantis DSM 15158* resulted in increased bacterial translocation (Osman et al 2006). In another animal study, reduced bacterial translocation to the liver and mesenteric lymph nodes in rats was noted when administered *Lactobacillus plantarum 299v* and treatment with oatmeal as the prebiotic did not prevent this (Mangell et al 2006). In a human study of 72 elective surgery patients, synbiotic feeding did not result in increased bacterial translocation (Anderson et al 2004).

SIGNIFICANT INTERACTIONS

Controlled studies are not available and at present there are no known drug interactions with prebiotics.

CONTRAINDICATIONS AND PRECAUTIONS

Prebiotics/synbiotics are contraindicated in those people who are hypersensitive to any component of the prebiotics/synbiotics-containing product. People with IBS who may have increased gas production should avoid high intakes of prebiotics (Serra et al 2001). People with lactose intolerance should use lactulose with caution.

PREGNANCY USE

Prebiotics found in the food chain are safe to consume in pregnancy.

PRACTICE POINTS/PATIENT COUNSELLING

- Prebiotics can be obtained from usual foods such as artichoke, asparagus, bananas, chicory, garlic, leek, onions, wheat.
- Prebiotics may be combined with probiotics to produce synbiotics that will enable the two components to work together in synergy.
- Although prebiotics may improve the long-term bowel flora, prebiotic supplementation has many other benefits not associated with direct colonisation of the gastrointestinal tract.
- There is some evidence that prebiotics support both the development and the maintenance of a healthy immune system.
- Prebiotics have been used in the management of diarrhoea, constipation, other gastrointestinal disorders, bone health, allergic disease and food sensitivity.
- Continuous intake of prebiotics is required in order to maintain their health benefits.
- Some individuals may experience greater gastrointestinal discomfort with use, although some symptoms may subside over time and dose reduction can improve tolerance

PATIENTS' FAQs

What will this supplement do for me?

Studies have shown that prebiotics are beneficial in the treatment of digestive disorders such as diarrhoea, constipation and some inflammatory bowel diseases and also other conditions, such as IBS, food

allergies and eczema. There is some evidence that prebiotics may be useful for bone health.

When will it start to work?

Usually prebiotics can exert beneficial effects for digestive disorders such as constipation and diarrhoea within 1–2 weeks, although continuous use for several weeks/months may produce long-term benefits and be necessary in the treatment of other disorders.

Are there any safety issues?

Generally, prebiotics have a good safety profile; however, high-dose supplements should be used under supervision in immunocompromised patients.

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Probiotics

HISTORICAL NOTE There is a long history of consuming fermented foods and beverages containing microorganisms to improve health. The term 'probiotic' is derived from Greek and means 'for life.' As far back as 1908, Metchnikoff, the Nobel laureate, stated that 'ingested lactobacilli can displace toxin-producing bacteria, promoting health and prolonging life' (Elmer 2001). The term 'probiotics' was first coined in 1965 and has since been applied to those live microorganisms that are able to promote health when consumed in sufficient quantities (FAO/WHO 2001). This is in contrast to the term 'prebiotics' which are dietary components. Although it has taken the most part of a century for scientists to investigate their health benefits, there are now several thousand studies published on probiotics, the majority published since 2000.

BACKGROUND AND RELEVANT PHARMACOKINETICS

At birth, the gastrointestinal tract is sterile but soon becomes colonised with microorganisms. The growth of normal gut flora is influenced by factors such as composition of the maternal gut microflora, diet, degree of hygiene, use of antibiotics or other medication, the environment and possibly genetic aspects. These microorganisms also confer health benefits by preventing the colonisation of the

Clinical note — Prebiotics and synbiotics
Prebiotics are components that modify the environment of the gastrointestinal tract to selectively favour proliferation of the beneficial intestinal microflora, lactobacilli and bifidobacteria (Gibson & Roberfroid 1995). Herbal and nutritional prebiotics include the fibre supplement known as slippery elm (*Ulmus fulva*), oligofructose and inulin. Synbiotics contain both pre- and probiotics.

gastrointestinal tract with pathogenic microorganisms. The gut bacteria also carry out a number of biochemical functions, including deconjugation and dehydroylation of bile acids, the conversion of bilirubin to urobilinogen, generation of short-chain fatty acids, the metabolism of cholesterol to coprostanol and production of vitamins K, B1, B2, B6 and B12 (Bengmark 1998, Hill 1997).

The gastrointestinal microflora is mostly resilient to change and remains fairly constant, although research over the years has shown that components such as pre- and probiotics can modulate the gut microflora. It has been estimated that the intestines are host to 10^{14} microbes representing 400–500 different species (Ouwehand et al 2002) and also includes yeasts, mostly *Candida albicans* (<0.1% of the microbiota) (Vandenplas et al 2007). This microflora has many important roles including enhancement of the gastrointestinal barrier function, nutrient metabolism, modulating immune function and producing potential health-promoting components (Bengmark 1998, Fotiadis et al 2008).

Probiotics can be obtained from the consumption of fermented foods as well as supplements. In order for a probiotic microorganism to show therapeutic effects, it must survive gastric acid and juices and bile salts, and should be viable in the digestive system. However, the majority of microorganisms ingested do not survive these conditions, and regular intake is required for successful colonisation (Goldin & Gorbach 1984).

Recently, the concept that probiotics should be viable/live has been evaluated. Studies have shown that bacterial DNA sequences may have similar effects as the live bacteria, and therefore, colonisation of the intestinal tract may not be a prerequisite for the action of probiotics (Jijon et al 2004, Rachmilewitz et al 2002). In addition, the mucosal immune system may not require direct contact with probiotics for beneficial effects as other routes of administration (such as the parenteral route) are also effective (Rachmilewitz et al 2004, Sheil et al 2004). However, there are also significant species and strain differences between the probiotic microorganisms, and therefore, they do not all share the same characteristics.

At present, there are numerous proposed uses of probiotics, and reports of their beneficial effects cover a wide range of diseases and conditions.

CHEMICAL COMPONENTS

Probiotics include bifidobacteria (e.g. *B. bifidum*); lactobacilli such as *L. acidophilus*, *L. bulgaricus*, *L. casei*, *L. gassen*, *L. plantarum*, *L. reuteri* and *L. GG* (variant of *L. casei* subsp. *rhamnosus*, named after Drs Gorbach and Goldin who first isolated the strain in 1980) and *Lactobacillus* strain LB; and Streptococci such as *Saccharomyces boulardii* (a yeast), *Streptococcus thermophilus* and *Streptococcus salivarius* (Hedin et al 2007).

FOOD SOURCES

Fermented foods, such as sauerkraut (Dedicatoria et al 1981) and kefir (Garrote et al 2001), are sources of probiotics. More commonly, dairy sources such as yoghurt may also contain probiotics, especially *L. acidophilus* and bifidobacteria strains.

DEFICIENCY SIGNS AND SYMPTOMS

Clear deficiency signs are difficult to establish because the symptoms may vary enormously. Local signs and symptoms of disruption of the intestinal microflora leading to an imbalance (intestinal dysbiosis) include bloating, flatulence, abdominal pain, diarrhoea and/or constipation and fungal overgrowth (such as *Candida*). An imbalance of gastrointestinal microflora can be caused by the use of antibiotics, and chronic diarrhoea or constipation. Administration of probiotics is used as a means of restoring this microflora imbalance (Bengmark 1998, Hedin et al 2007, Hoveyda et al 2009, Kajander et al 2008, McFarland 2006, 2007, McFarland & Dublin 2008).

MAIN ACTIONS

Numerous mechanisms have been proposed by which probiotics could exert their health-promoting effects.

Immune modulation

Immune system modulation and the prevention of gastrointestinal tract colonisation by a variety of pathogens are among the most important actions of probiotics.

Probiotics compete for receptor sites that prevent adhesion of pathogenic bacteria to the gut wall and produce inhibitory substances such as bacteriocins, lactic acid and toxic oxygen metabolites. Of the toxic oxygen metabolites, hydrogen peroxide is of major importance as it exerts a bactericidal effect on many pathogens (Kaur et al 2002). The ability to produce bacteriocins, hydrogen peroxide and other antimicrobial compounds is strain dependent and requires the presence of folic acid and riboflavin in the case of lactobacilli. Binding to the gut wall also initiates signalling events that result in the synthesis of cytokines (Vanderhoof & Young 2003). Studies in germ-free mice have proven that intestinal bacteria are essential for a healthy systemic immune system (Falk et al 1998).

Probiotics may also produce anti-inflammatory components, decrease the luminal pH, compete for nutrients with potential pathogens and as a result of inhibitory substances produced by probiotics. These antimicrobial substances produced by probiotics include bacteriocins, lactic acid and hydrogen peroxide (Kaur et al 2002).

A growing body of evidence indicates that in particular lactobacilli and bifidobacteria can

modulate the immune system at both the systemic and the mucosal level affecting many cell types (e.g., epithelial cells, dendritic cells, natural killer cells, etc). Consequently, health benefits induced by probiotics include the stabilisation of the microflora, enhancing the mucosal defence effects via tight junction integrity between enterocytes and downregulating proinflammatory cytokines (e.g. tumour necrosis factor alpha), and inducing regulatory cytokines (plus interleukin (IL)-10 and transforming growth factor-beta) as reported in patients with inflammatory bowel disease (IBD) (Borruel et al 2002, Pathmakanthan et al 2004). However, these probiotic-induced immunomodulatory characteristics are species and strain specific.

Gastrointestinal effects

Probiotic therapy has been shown to be beneficial in promoting healthy digestive function, eradicating various gastrointestinal infections and managing gastrointestinal diseases.

Helicobacter pylori infection

Several in-vitro studies have shown that certain probiotics inhibit or kill *H. pylori*, prevent its adhesion to mammalian epithelial cells and prevent IL-8 release. In-vivo models demonstrate that pretreatment with a probiotic can prevent *H. pylori* infections and/or that administration of probiotics markedly reduces an existing infection. Clinical efficacy has also been evaluated for the use of probiotics as prevention or treatment and has shown promising results according to a review of six clinical studies (Hamilton-Miller 2003).

Probiotics such as *Lactobacillus* spp exhibit antimicrobial effects against *H. pylori* infection of the gastric mucosa by releasing bacteriocins and limiting adhesion to epithelial cells (Gotteland et al 2006).

Inflammatory bowel disease

This is characterised by alterations in gastrointestinal microflora with reports of increased bacteroides, *Escherichia coli* and enterococci and reduced lactobacilli bifidobacteria (Neut et al 2002, Swidsinski et al 2002). As treatment with probiotics is associated with restoring colonic microbiota and decreasing inflammation, this has been investigated in a number of gastrointestinal disorders, including IBD and antibiotic associated diarrhoea.

Chemopreventative effects

Select probiotics may have anticancer properties. Different strains of *Lactobacillus acidophilus* and bifidobacteria have been studied to investigate their antimutagenic activity against chemical mutagens (Lankaputhra & Shah 1998).

Antimutagenic activity against chemical mutagens and promutagens has been demonstrated for different strains of *Lactobacillus acidophilus*, bifidobacteria and the organic acids usually produced by these probiotics, with live cells producing the most positive results (Lankaputhra & Shah 1998). Some probiotics also reduce faecal enzymes implicated in cancer initiation, by producing butyric acid, which affects the turnover of enterocytes and neutralises the activity of dietary carcinogens, such as nitrosamines. Additionally, enhancing host immunity and qualitative and quantitative changes to the intestinal microflora and physicochemical conditions are important contributing factors (Hirayama & Rafter 1999).

OTHER ACTIONS

Several clinical studies have investigated lipid-lowering activity of probiotics (See *Clinical use* below).

CLINICAL USE

It is generally agreed that a probiotic must be capable of colonising the intestinal tract to influence human health. Currently, one of the most extensively studied probiotics is *Lactobacillus GG*. Probiotic supplements are usually standardised in terms of the amount of living organisms per unit of volume, and dosages range from 1 billion colonies to as high as 450 billion daily.

Gastrointestinal infections

Probiotics may have a role in the management of various infections and particularly gastrointestinal infections, such as bacterial induced diarrhoea, *Helicobacter pylori*, recurrent *Clostridium difficile*-associated disease and pancreatitis.

Diarrhoea

Various probiotic strains have been subjected to clinical trials to evaluate their efficacy in diarrhoea of different origins.

Infectious diarrhoea

A Cochrane review analysed results from 23 randomised controlled trials (RCTs) ($n = 1917$) evaluating the role of probiotic agents in acute diarrhoea proven or presumed to be caused by an infectious agent (Allen et al 2004). The majority of subjects were infants or children ($n = 1449$; age < 18 years). The review concluded that probiotics reduced the risk of diarrhoea at 3 days, and the mean duration of diarrhoea by 30.5 h and supplementation was a useful adjunct to rehydration therapy in treating acute, infectious diarrhoea in adults and children. Several different probiotics were tested: all were lactic acid bacilli, except in two studies that tested the yeast *Saccharomyces boulardii*. With the exception of a trial of live *Streptococcus thermophilus* and *Lactobacillus bulgaricus*, a beneficial effect in the probiotic group compared to controls was observed in all trials.

Many double-blind, prospective, randomised trials that utilised *S. boulardii* in children with acute gastroenteritis have demonstrated a significant improvement (Vandenplas et al 2007).

A more recent meta-analysis of eight RCTs ($n = 988$) by Szajewska et al (2007) concluded that although there was no reduction in the number of stools for any given time period, the duration of diarrhoea was much shorter as a result of *Lactobacillus GG* treatment; however, the authors noted that the heterogenicity and methodological considerations of the studies limited the strength of the conclusion.

In order to determine the dose-dependent effect of *Lactobacillus GG* on faecal rotavirus shedding, Fang et al (2009) conducted an open-label randomised study where 23 children with rotavirus gastroenteritis were treated for 3 days with a daily dose of LGG 0 colony-forming units (CFU)/day (control group, $n = 6$) or administered 2×10^8 CFU/day (low-dose group, $n = 9$) or 6×10^8 CFU/day (high-dose group, $n = 8$). The results of this study demonstrated that the high-dose probiotic group was the only group who experienced a significant reduction of rotavirus levels in stool samples (86% after 3 days).

Due to the differing findings from studies in this area, further investigation is required in order to confirm/clarify the most appropriate probiotic strains to be used, optimal dosage and length of time for treatment. Most findings agree that treatment with certain probiotic strains (e.g. *S. boulardii*, *L. casei GG*, *L. acidophilus*, *L. bulgaricus* and *L. reuteri*) result in a 24-h (17–30 h) reduction in diarrhoea duration, and the beneficial effects are more pronounced if administered early in the illness (Vandenplas et al 2007).

Travellers' diarrhoea

Travellers' diarrhoea is the most common health problem in those visiting developing countries, affecting 20% to more than 50% of tourists. Although it is usually benign, travellers' diarrhoea represents a considerable socioeconomic burden for both the traveller and the host country. The most common enteropathogen is *Escherichia coli*, although a number of other microorganisms are also implicated.

Some clinical studies have found various probiotics somewhat effective against travellers' diarrhoea; however, no probiotic has been able to demonstrate clinically relevant protection worldwide (Rendi-Wagner & Kollaritsch 2002).

A large, randomised, placebo-controlled, double-blind study of the efficacy of *Lactobacillus GG* in preventing travellers' diarrhoea involved 820 people on holiday to Turkey to two destinations. The group was randomly assigned either *L. GG* or placebo in identical sachets. On the return flight, each participant completed a questionnaire indicating the incidence of diarrhoea and related symptoms during the trip. Of the original group, 756 (92%) subjects completed the study. The overall incidence of diarrhoea was 43.8% (331 cases), and the total incidence of diarrhoea in the *L. GG* group was 41.0% compared with 46.5% in the placebo group, indicating an overall protection of 11.8%. Protection rates varied between two different destinations, with the maximum protection rate reported as 39.5% and no side effects reported (Oksanen et al 1990).

In another placebo-controlled double-blind study, two doses (250 and 1000 mg) of *Saccharomyces boulardii* were administered prophylactically to 3000 Austrian travellers. A significant reduction in the incidence of diarrhoea was observed, with success depending directly on the rigorous use of the preparation. A tendency was noted for *S. boulardii* to have a regional effect, which was particularly marked in North Africa and in Turkey. The effect was dose dependent, with participants taking the higher dose of probiotics experiencing the lowest incidence of travellers' diarrhoea (29%) and little difference observed between low-dose *S. boulardii* supplementation (34%) and placebo (39%). Treatment was considered very safe (Kollaritsch et al 1993).

Positive results were confirmed more recently in a meta-analysis of 12 randomised, controlled clinical trials that investigated the role of probiotics in the prevention of travellers' diarrhoea (McFarland 2007). The authors concluded that probiotics significantly prevent travellers' diarrhoea (RR = 0.85, $P < 0.001$), and *Saccharomyces boulardii* and a mixture of *Lactobacillus acidophilus* and *Bifidobacterium bifidum* demonstrate the major beneficial effects.

Antibiotic-induced diarrhoea

A recent Cochrane review by Johnston et al (2007) assessed the efficacy of probiotics for the prevention of antibiotic associated diarrhoea in children (0–18 years). Although per protocol analysis was positive for the use of probiotics in reducing diarrhoea, these findings were not significant in the intention to treat analysis and the routine use of probiotics could not be recommended. Recommendations were made for future research using probiotics most likely to be useful agents such as *Lactobacillus GG*, *Lactobacillus sporogenes* and *Saccharomyces boulardii* at 5–40 billion CFU/day.

Previously, a meta-analysis (D'Souza et al 2002) which assessed nine randomised, double-blind, placebo-controlled trials came to a positive conclusion. Four of the studies tested the yeast *S. boulardii*, four used lactobacilli, one used a strain of enterococcus-producing lactic acid and in three studies a combination of probiotics was administered. Overall, *Lactobacillus* spp. and *Saccharomyces boulardii* were reported to be effective in preventing antibiotic associated diarrhoea.

Clostridium-difficile-associated diarrhoea (CDAD)

Clostridium difficile is a common cause of diarrhoea associated with treatment with antimicrobial and/or antibiotic medication and can potentially progress to colitis, pseudomembranous colitis, toxic megacolon and death. In spite of antimicrobial therapy, recurrence is common, and increasingly, probiotic supplementation has been investigated as a potential treatment for CDAD.

A meta-analysis by McFarland (2006) assessed six blinded randomised controlled trials ($n = 354$ patients) that used a mixture of probiotics in the management of *Clostridium difficile*-associated diarrhoea (CDAD). The results showed that only *S. boulardii* supplementation resulted in a significant reduction in recurrence. These findings are in contrast to an earlier meta-analysis by Dendukuri et al (2005), where a role for probiotic use in CDAD was not supported in all the studies; the authors reported methodological flaws in some of the studies although some benefit of probiotic therapy was seen in patient subgroups, particularly those characterised by severe CDAD and high use of vancomycin.

AIDS-related diarrhoea

In a small study, 24 women with AIDS/HIV, aged 18–44 years, who were not being treated with antiretrovirals and had moderate diarrhoea, were given either a yoghurt fermented with *Lactobacillus delbruekii* var *bulgaricus* and *Streptococcus thermophilus*, supplemented with probiotic *Lactobacillus rhamnosus* GR-1 and *L. reuteri* RC-14 or an unsupplemented yoghurt for 15 days. Women receiving the supplemented probiotic–yoghurt experienced less diarrhoea, flatulence and nausea than those receiving the unsupplemented yoghurt (Anukam et al 2008).

S. boulardii has also been used for HIV diarrhoea (Saint-Marc et al 1991). Trois et al (2008) investigated the effect of probiotics on the immune response in a randomised, double-blind, controlled trial of two groups of children (2–12 years) infected with HIV. The study of 77 children administered either a formula containing *Bifidobacterium bifidum* + *Streptococcus thermophilus* −2.5 × 10^{10} CFU or a standard formula on a daily basis for 2 months. At the end of the study, there was an increase in CD4 cell count suggestive of improved immune response.

Irritable bowel syndrome

People suffering from irritable bowel syndrome (IBS) sometimes experience symptoms of abdominal cramping and either diarrhoea or constipation or a combination of both. They can also experience symptoms of abdominal distension, cramping and pain. Although the aetiology of IBS is still unknown, there is growing suspicion that there is a persistent, mild inflammatory state with changes in mucosal function or structure and an associated imbalance of intestinal flora (Camilleri 2006). This imbalance can lead to inefficient metabolism of nutrients and the formation of gas and short-chain fatty acids, both of which induce propulsive contractions and accelerate colonic transit or enhance fluid and sodium absorption in the colon. As such, clinical trials have been conducted to clarify the role of probiotics in this condition, so far producing promising results.

A 2008 meta-analysis concluded that probiotics can result in improved symptom relief in the treatment of IBS (McFarland & Dublin 2008). Twenty randomised controlled clinical trials ($n = 1404$) were reviewed, and either single or multiple probiotics were used for varying time periods ranging from 2 to 24 weeks (median = 4 weeks); overall, there were insufficient data to draw conclusions about the most effective probiotic strains or the assessment of individual IBS symptoms.

Similarly, a 2009 systematic review and meta-analysis by Hoveyda et al (2009) reported that probiotic therapy for several weeks may result in modest improvement in overall symptoms of IBS. A total of 14 randomised placebo-controlled trials of varying length (from 4 weeks to 6 months although the majority lasted 8 weeks or less) of the intervention period were included in the analyses; the probiotic therapy varied in the type of probiotics used as well as the dose and strength; in addition, some studies used a single agent and others used combinations of multiple microorganisms.

Most recently, Kajander et al (2008) conducted a randomised, placebo-controlled study for 5 months and investigated the effects of a daily dose of a multispecies probiotic supplement (*Lactobacillus rhamnosus GG*, *L. rhamnosus* Lc705, *Propionibacterium freudenreichii* ssp. *shermanii* JS and *Bifidobacterium animalis* ssp. *lactis* Bb12) in 86 patients with IBS. Active treatment resulted in relief from IBS symptoms (especially distension and abdominal pain) and stabilisation of the intestinal microflora compared with placebo.

Similarly, earlier studies had reported favourable results with supplementation of *L. plantarum* for 4 weeks in successfully treating symptoms of IBS and improving bowel function (Nobaek et al 2000, Niedzielin et al 2001).

Not all clinical studies have produced positive results. A large randomised, parallel group, double-blind study by Drouault-Holowacz et al (2008) investigated the effects of four strains of lactic acid bacteria on symptoms of IBS in 100 patients over a 4-week period. Overall, there was little difference between the two groups, although some improvement was noted regarding abdominal pain and stool frequency in some patient subgroups.

Some of the reported differences of the effects of probiotics regarding IBS-related symptoms may be due to strain differences; it has been suggested that encapsulated *Bifidobacterium infantis* 35624 (dose: 10^8) may be more suitable than *Lactobacillus* (O'Mahony et al 2005, Whorwell et al 2006). Rousseaux et al (2007) demonstrated that oral administration of *L. acidophilus* induced expression of mu-opioid and cannabinoid receptors in human intestinal epithelial cells.

Helicobacter pylori infection

Helicobacter pylori was first discovered in the early 1980s. At that time, triple therapy was advocated and used effectively as a treatment. This consisted of antibiotics, clarithromycin, amoxicillin or metronidazole and proton pump inhibitor, but in recent years, the standard triple therapies have not been so successful. Additionally, triple therapy has been associated with unfavourable side effects such as antibiotic associated diarrhoea. Consequently, there have been attempts to investigate alternative therapies. Generally, studies have found probiotics reduce gastrointestinal symptoms and the side effects of triple therapy; however, findings have been mixed regarding the effect of probiotics on *Helicobacter pylori* eradication (Egan et al 2007). It has been proposed that the different results obtained in studies may be because only some, but not all, strains of probiotics are effective against *H. pylori* (Gotteland et al 2006).

Park et al (2007) studied the effect of *Bacillus subtilis* and *Streptococcus faecium* as probiotic supplements on *H. pylori* eradication in a randomised study. The study of 352 *H. pylori*-positive patients compared standard triple therapy plus probiotics to triple therapy as stand-alone treatment. After an 8-week intervention period, both patient groups were followed up for a further 4 weeks. The group receiving combination therapy with adjunctive probiotics

experienced less diarrhoea than standard treatment and also showed a higher eradication rate (83.5 vs 73.3%, $P = 0.027$) in comparison to the usual care group. The same year, a double-blind randomised placebo-controlled crossover study by Imase et al (2007) utilised *Lactobacillus reuteri* strain SD2112 tablets in the management of 33 patients infected with *H. pylori* and asymptomatic volunteers. Once again, probiotic treatment was effective in suppressing *H. pylori* infection.

The same researchers also investigated a *Clostridium butyricum* preparation (CBM588) as a potential eradication therapy for *H. pylori* in a study of 19 patients who were randomised to receive regular doses of CBM588, or double doses of CBM588, and a group that was not treated with this probiotic. The results were favourable for the use of the probiotic; diarrhoea was absent in the group that was treated with double doses of CBM588, and in addition, *C. difficile* toxin A could not be detected (Imase et al 2008).

In contrast, a recent pilot study of 65 dyspeptic patients with confirmed *H. pylori* infection investigated the potential beneficial effects of *Lactobacillus reuteri* (*L. reuteri*) or a high concentration of probiotics in addition to the standard triple therapies for eradication of the infection and found all treatments to be ineffective. The participants received a standard 7-day triple therapy, or standard treatment plus *L. reuteri* supplementation, or they received the same 7-day triple therapy plus a probiotic mixture or a 14-day standard triple therapy plus a probiotic mixture. The authors reported that 4–6 weeks after treatment, the 7–14-day triple therapy with or without probiotic supplementation failed to achieve acceptable *H. pylori* eradication rates (Scaccianoce et al 2008).

In a small, double-blind, placebo-controlled study of 40 patients with *H. pylori* infection, *Lactobacillus reuteri* ATCC 55730 supplements or placebo was administered once a day for 4 weeks; the probiotic-treated group reported significantly less gastrointestinal symptoms ($P < 0.05$) compared to their pretreatment status. However, the probiotic treatment did not affect the eradication rates (Francavilla et al 2008).

Gotteland et al (2008) investigated the potential for an additive or synergistic inhibitory effect of cranberry juice and *Lactobacillus johnsonii* La1 (La1) in the management of *H. pylori* infection in children. The multicentric, randomised, controlled, double-blind study of 295 children aged 6–16 years compared four different treatments: cranberry juice plus viable La1, cranberry juice plus nonviable La1, placebo juice plus viable La1 or placebo juice plus nonviable La1 (untreated controls). All groups consumed their juice plus probiotic on a daily basis for 3 weeks. Treatment with either cranberry juice or La1 was successful and produced significant differences ($P < 0.01$) in eradication rates compared to the control group; however, no synergistic effect was noted when cranberry juice and probiotics were combined.

Surprisingly, a large randomised study of 347 patients with *H. pylori* infection found that when standard care was combined with a yoghurt supplemented with *Lactobacillus acidophilus* HY2177, *Lactobacillus casei* HY2743, *Bifidobacterium longum* HY8001 and *Streptococcus thermophilus* B-1, a greater incidence of side effects was reported. Adverse effects included diarrhoea and having a metallic taste in the mouth (69/168) compared to the standard care group 26.3% (47/179) ($P = 0.003$) (Kim et al 2008). Adjunctive probiotic treatment did not improve eradication rates beyond standard care in the study.

In contrast, in a recent prospective open study (Hurduc et al 2009), 90 symptomatic children (aged 3–18 years) with *H. pylori* infection were randomised into two groups: one group ($n = 48$) was treated with *Saccharomyces boulardii* (250 mg b.i.d., for 4 weeks) and the other group ($n = 42$) served as the control group; all the children were treated with the standard triple eradication therapy (omeprazole/esomeprazole, amoxicillin and clarithromycin) for 7–10 days. After 4–6 weeks, there was little difference in the eradication rate (control = 80.9%, *S. boulardii* group = 93.3%; no significant difference). However, *S. boulardii* plus the standard eradication treatment resulted in a significant reduction in the incidence of side effects (30.9 vs 8.3% in the probiotic group; $P = 0.047$).

Inflammatory bowel disease

Probiotics are also being used as adjunctive therapy for Crohn's disease (CD) and IBD (Goh & O'Morain 2003, Guslandi 2003a, 2003b, Kanauchi et al 2003, Karthik 2003, Marteau et al 2003, Rutgeerts 2003). Due to differences in study design, number of participants and dose and strain of probiotic used, it is difficult to assess the role of probiotics in IBD. Overall, present research indicates a limited role for probiotics in CD, the results for ulcerative colitis (UC) are more promising, and there does seem to be a beneficial effect in pouchitis.

Crohn's disease

Only a limited number of studies have indicated a role for probiotics in the remission of CD. In one study, Guslandi et al (2000) compared *S. boulardii* plus mesalazine with mesalazine alone and found that adjunctive probiotic treatment resulted in fewer relapses.

Supplementation with VSL#3 has also been evaluated. VSL#3 contains a high concentration of eight strains of lactic acid bacteria, including *B. breve*, *Bifidobacterium longum*, *B. infantis*, *L. acidophilus*, *L. plantarum*, *L. casei*, *Lactobacillus bulgaricus* and *Streptococcus thermophilus*. A study of 40 patients randomised to 3 months of rifaximin followed by 9 months of VSL#3 or to 12 months of mesalazine also reported relapse prevention with probiotic therapy (Campieri et al 2000).

The majority of other studies, including randomised double-blind placebo-controlled trials, have not confirmed the utility of LGG or *Lactobacillus johnsonii* La1 in the remission of CD (Hedin et al 2007). Similarly, studies that have administered probiotics for the treatment of active CD have also provided mixed results and mainly because of

concurrent use of medications during the intervention period (e.g., prednisolone use or metronidazole) (Gupta et al 2000).

A Cochrane systematic review by Rolfe et al (2006) did not advocate a role for probiotics in CD based on the available evidence, suggesting that because all studies enrolled small numbers of patients, they may have lacked statistical power to show differences should they exist. Seven RCTs were identified that had utilised a variety of probiotics such as *Lactobacillus GG*, *E. coli* Nissle and *Saccharomyces boulardii*; most of the studies had a relatively small number of participants with different treatment protocols, probiotics and outcome measures, making it difficult for comparisons to be made.

Ulcerative colitis

A number of studies have assessed probiotic supplementation for the remission of UC, with probiotics such as lactobacilli or bifidobacteria being found to be ineffective, while *Escherichia coli* Nissle 1917 was reported to be as beneficial as and similar in terms of effectiveness to 5-aminosalicylic acid (Hedin et al 2007).

The role of probiotic therapy during active UC has been confirmed in some studies; clinical benefit of VSL#3 was noted in a few studies. Some investigators have used *E. coli* Nissle 1917 enemas in left-sided UC for direct delivery of the probiotic and others have used probiotic mixtures (*B. breve* strain Yakult, *B. bifidum* strain Yakult and a *L. acidophilus* strain) in fermented milk (Hedin et al 2007).

Pouchitis

Probiotics have also been used in patients with relapsing or chronic pouchitis (Kailasapathy & Chin 2000). While studies have produced inconsistent results, overall there appears to be some evidence to support the therapeutic use of probiotics in postoperative pouchitis (Penner et al 2005) and the general view is that VSL#3 treatment can be effective in controlling this condition.

Studies by Gionchetti et al (2000, 2003) assessed the use of VSL#3 in both primary prevention of pouchitis and maintenance therapy for chronic relapsing pouchitis, demonstrating some success. In their randomised, controlled, double-blind study, 40 patients with relapsing pouchitis in remission received a 6-g daily dose of VSL#3 or a placebo for 9 months. Probiotic treatment resulted in a significantly reduced incidence of pouchitis (Gionchetti et al 2000), but when VSL#3 treatment was ceased, all patients relapsed 3 months later. In a subsequent randomised controlled study to investigate VSL#3 treatment for primary prophylaxis of pouchitis in 40 patients, Gionchetti et al (2003) reported that treatment with VSL#3 resulted in fewer relapses.

In another randomised, double-blind, controlled trial, Mimura et al (2004) also utilised VSL#3 in 36 patients with more severe recurrent pouchitis over a 1-year follow-up period and reported good results regarding maintenance of remission and improved quality of life in the patients.

A combination of probiotics also has been reported to result in beneficial effects; lactobacilli and bifidobacteria in fermented milk were administered to patients who had pouchitis after UC surgery, resulting in some resolution of disease activity (Laake et al 2005).

In contrast, in an uncontrolled study of 31 patients who were treated with antibiotics and were in remission, Shen et al (2005) found little benefit with VSL#3 administered for 8 months.

Probiotics and diverticular disease

It has been suggested that altered bacterial flora is one of the causes of diverticular inflammation (White 2006). Consequently, some investigators have evaluated the role of probiotics in diverticular disease. In an open-label study, 15 patients with diverticular disease were treated with an antimicrobial and charcoal for the first symptomatic episode after enrolment and the second episode was treated with the same therapy followed by *Escherichia coli* Nissle 1917 for 6 weeks. This second treatment resulted in a longer symptom-free duration of a mean of 14 months compared to a mean of 2.4 months in the control group (Fric & Zavoral 2003).

Various studies have attempted to restore the altered microflora using probiotics, but most of these studies have been limited in their design and methods (Sheth & Floch 2009). However, results from these studies appear to be mostly positive, and randomised placebo-controlled studies are needed in order to make recommendations.

Pancreatitis

Probiotic therapy has been investigated in pancreatitis because of the increased risk of bacterial infections. Some animal studies have shown that the use of *L. plantarum* 299v (Mangiante et al 2001) and *S. boulardii* (Akyol et al 2003) reduced bacterial translocation. Human studies have investigated the use of single probiotic agents such as live *L. plantarum* 299v given to 22 patients compared with an inactivated form given to 23 patients; the probiotic-supplemented group had reduced rates of infection and abscess formation (Olah et al 2002). However, these findings are in contrast to those of Besselink et al (2008) (see *Adverse reactions*).

Alcohol-induced liver disease

In a prospective, randomised, clinical study, 66 men with advanced alcohol-induced liver disease received either *Bifidobacterium bifidum* and *Lactobacillus plantarum* 8PA3 or standard therapy (no probiotics) for 5 days. At the end of the study, patients who had received the probiotic therapy had significantly increased numbers of both bifidobacteria (7.9 vs 6.81 log CFU/g) and lactobacilli (4.2 vs 3.2 log CFU/g) compared to the standard therapy group; likewise, the former group had a significant improvement in hepatic enzyme levels (Kirpich et al 2008).

Hepatic encephalopathy

To date, there are only a few reports about the role of probiotics in hepatic encephalopathy; in addition to the conventional management with antibiotics

and lactulose, probiotics may confer favourable changes in intestinal microflora in patients with hepatic encephalopathy.

A recent randomised, controlled, single tertiary centre study with open allocation by Bajaj et al (2008) investigated the effects of probiotic administration on minimal hepatic encephalopathy (MHE), a preclinical stage prior to full-blown hepatic encephalopathy. The probiotics *S. thermophilus*, *L. bulgaricus*, *L. acidophilus*, bifidobacteria and *L. casei* were administered in a yoghurt to a group of patients for 60 days; the study demonstrated a significant rate of MHE reversal.

Colon cancer

A number of factors may be involved in colon cancer risk, and it has been suggested that the colonic microflora may be involved in the aetiology of colorectal cancer. A lower incidence of colon cancer has been associated with the consumption of lactobacillus or bifidobacteria, but the exact mechanism has not been elucidated (Fotiadis et al 2008).

Atopic dermatitis and eczema

It has been widely reported that during the first few months of life, exposure to high-level antigens may predispose some individuals to allergic sensitisation and therefore various atopic conditions. Intestinal microflora plays a major protective role against the development of allergy because it reduces antigen transport through the intestinal mucosa. Consequently, probiotics may have a protective role in the prevention and/or management of atopic dermatitis (AD) and eczema because of their proposed actions (Rosenfeldt et al 2004).

Many clinical studies have investigated probiotic therapy to prevent allergic disease, and some have reported a reduction in the severity of the condition (Furrie 2005, Weston et al 2005).

Prevention of allergy

An early randomised, double-blind, placebo-controlled study showed that perinatal administration of probiotics (*L. rhamnosus GG*) reduced the development of atopic eczema in children by 50% during the first 2 years of life. Some 159 mothers were randomly allocated to receive 2 capsules of placebo or 10^{10} viable *L. rhamnosus GG* daily for 4 weeks before expected delivery. After delivery, capsules were taken for 6 months. During lactation, either the mother or the infant consumed the preparations. In a 4-year follow-up study, it was revealed that the preventive effect of the probiotic on atopic eczema extended beyond infancy (Kalliomaki et al 2003).

The role of probiotics in the prevention and treatment of paediatric AD was reported recently in a meta-analysis by Lee et al (2008); 21 trials were assessed (n = 1898; age: 0–13 years) and analysis of the findings supported a role in prevention of paediatric AD rather than treatment.

Treatment of established allergy

A randomised, double-blind study of 56 young children (aged 6–18 months) with moderate or severe atopic AD found that treatment with *L. fermentum* VRI-033 PCC (1×10^9; Probiomics) twice daily produced a significant reduction in the Severity Scoring of Atopic Dermatitis (SCORAD) index (Weston et al 2005). At week 16, 92% of children receiving probiotics had a SCORAD index that was significantly better than baseline compared with the placebo group (n = 17, 63%) (P = 0.01). Another randomised double-blind study has found that supplementation of infant formulas with viable but not heat-inactivated *L. GG* may have benefits for the management of atopic eczema and cow's milk allergy (Kirjavainen et al 2003).

According to two other placebo-controlled studies, it appears that people with greater allergic responses may be better suited to treatment and experience superior effects. Rosenfeldt et al found that treatment with two *Lactobacillus* strains (lyophilised *L. rhamnosus* 19070-2 and *L. reuteri* DSM 122460) given in combination for 6 weeks to children aged 1–13 years with AD resulted in 56% experiencing improvement (Rosenfeldt et al 2003). Interestingly, the total SCORAD score did not change significantly. Allergic patients with a positive skin prick test response and increased IgE levels experienced a more pronounced response to treatment.

Similarly, a study by Sistek et al (2006) found that a combination of two probiotics (*Lactobacillus rhamnosus* and *Bifidobacterium lactis*) given to children with established AD effectively reduced the SCORAD index among the food-sensitised children, but not in other children. Children in this study received 2×10^{10} CFU/g of probiotic or placebo daily as a powder mixed with food or water.

In contrast, a randomised, double-blind, placebo-controlled trial by Taylor et al (2007) utilising *L. acidophilus* for the first 6 months of life did not find a reduction in the risk of AD in high-risk infants, and in fact the treatment was associated with significantly increased allergen sensitisation. The study was completed by a total of 178 mothers and their healthy full-term infants (n = 89 probiotic and n = 89 control). At 1 year of age, infants were clinically assessed for AD, food allergy and/or sensitisation. Potential confounders, such as differences in birth length and birth head circumference, antibiotic usage, play group attendance and daycare attendance, were considered in the final analyses. The conflicting results of this study in comparison to earlier findings may be due to many factors including differences in probiotics used, i.e. *Lactobacillus rhamnosus GG* compared to *L. acidophilus* LaVRI-A1, maternal diet regarding consumption of fermented foods, maternal and other family members at risk of AD, food allergy and/or sensitisation, differences in how the infants received the probiotic treatment and the time of the clinical measures.

In a recent double-blinded, placebo-controlled study by Kuitunen et al (2009), pregnant mothers (n = 1223) whose offspring were at increased risk for allergy were given either a probiotic mixture (2 lactobacilli, bifidobacteria and propionibacteria) (n = 610) or placebo during the last month of pregnancy (n = 613). After birth, the infants of the mothers who took probiotics also received the

probiotics with a prebiotic galacto-oligosaccharide for 6 months. The other infants received a placebo. After 5 years, the cumulative incidence of allergic diseases (eczema, food allergy, allergic rhinitis and asthma) and IgE sensitisation was determined in 891 (88%) infants (n = 445 in the intervention group, n = 446 in the control group). Perinatal probiotic supplementation did not confer any significant benefits in preventing allergy as there was little difference in any of these parameters, but interestingly, in caesarean-delivered children receiving probiotics, less IgE-associated allergic disease was reported (P = 0.035), indicating a protective effect.

High cholesterol

Some probiotics may have cholesterol-lowering effects due to several mechanisms including enzymatic deconjugation of bile acids and metabolic utilisation of cholesterol (Brashears et al 1998, Liong & Shah 2005).

According to a meta-analysis of six studies of a probiotic dairy product containing *Enterococcus faecium*, treatment with the fermented yoghurt product produced a 4% decrease in total cholesterol and a 5% decrease in low-density lipoprotein cholesterol (Agerholm-Larsen et al 2000).

Since then, mixed findings have been reported regarding the use of encapsulated probiotics; a hypocholesterolaemic effect was not observed in some studies (Lewis & Burmeister 2005, Larsen et al 2006, Simons et al 2006, Greany et al 2008, Hatakka et al 2008), but Hlivak et al (2005) provided a daily dose of 10^9 CFU of probiotic bacteria and noted a hypocholesterolaemic effect. It is possible that lipid-lowering activity induced by probiotics is dependent on whether patients have high cholesterol levels (>6.0 mmol/L) (Agerback et al 1995, Bertolami et al 1999, Hlivak et al 2005, Xiao et al 2003) or lower to normal cholesterol levels (<5.4 mmol/L) (de Roos et al 1999, Greany et al 2004), although further randomised trials are required to confirm this observation.

Most recently, two randomised, placebo-controlled studies failed to detect a significant lipid-lowering activity for different strains of probiotics. Greany et al (2008) conducted a randomised, single-blinded, placebo-controlled, parallel-arm study of 33 normocholesterolaemic women and 22 men aged 18–36 years. Subjects in the intervention group were treated for 3 months with probiotic capsules (3 capsules daily) containing a total of 10^9 CFU *Lactobacillus acidophilus* strain DDS-1 and *Bifidobacterium longum* strain UABL-14 and 10–15 mg fructo-oligosaccharide. These probiotic strains had no effect on plasma lipid concentrations (Greany et al 2008).

Likewise, Hatakka et al (2008) conducted a double-blind, randomised, placebo-controlled, two-period crossover study to investigate the effects of taking on a daily basis two probiotic capsules containing viable *Lactobacillus rhamnosus* LC705 and *Propionibacterium freudenreichii* ssp *shermanii* JS (2×10^{10}

Clinical note — The hygiene hypothesis

The intestinal tract is the largest immune organ of the body. It produces more antibodies than any other part of the body and contains 80% of all antibody-producing cells. The intestinal mucosa functions as a barrier against infections, but it also provides communication between the different mucosal surfaces of the body (Ouwehand et al 2002).

At birth, the gastrointestinal tract is sterile. Normal gut flora develops gradually over time and is influenced by factors such as composition of the maternal gut microflora, diet, degree of hygiene, use of antibiotics or other medication, the environment and possibly genetic aspects. Studies in germ-free mice have shown that without these bacteria, the systemic immune system will not function normally (Vanderhoof & Young 2002).

In the absence of microbes, a mammal develops fewer Peyer's patches (part of the gut-associated lymphoid tissue) and less than 10% of the number of IgA-producing B cells compared with normal. However, on exposure to a normal microflora, previously germ-free animals develop their immune system very much like other animals. This indicates that the intestinal microflora is instrumental in the proper development of the immune system (Ouwehand et al 2002) and has led to the emergence of the 'hygiene theory of immune disorders'.

More specifically, the hygiene hypothesis suggests that improved hygienic conditions and vaccinations, which reduce early-life exposure to microbes, are associated with a heightened risk of allergic disease and other immune disorders. This is because reduced exposure may result in reduced stimulation of the immune system. As a result, lymphocytes that would normally differentiate to become Th1 type differentiate to Th2-type cells and produce inflammatory cytokines in the allergic response in much greater quantities. As such, very early stimulation of the immune system is important in dampening the Th2 dominance and reducing the development of IgE-mediated food reactions as well as other allergic reactions. In a closely observed cohort of 329 Finnish children, it was shown that the earlier an acute respiratory infection occurred, the greater the protective effect was against atopic eczema (Vanderhoof & Young 2003).

The obvious solution for increasing microbial exposure without increasing the health risk is the use of prebiotics and probiotics. Supplementation with probiotics has been shown to both reduce the risk and treat the symptoms of childhood eczema (see later).

Modulating the intestinal microflora with probiotics and prebiotics (fibre) may be an effective and safe therapy for the natural development of a balanced immune defence in infants and children. In adults and the elderly, prebiotics and probiotics may be used to improve the general functioning of the immune system.

CFU of each strain) on serum cholesterol and triglyceride levels: the study of 38 mildly or moderately hypercholesterolaemic men aged 24–55 years found that probiotic treatment over 4 weeks did not have any effect on serum lipids.

Urogenital infections

Probiotics are widely used in active treatment of urogenital infections and to decrease the frequency of recurrent bacterial vaginosis and candidal vulvovaginitis. They are administered both orally and locally with several small trials supporting their use.

Recent studies using molecular typing have confirmed that oral intake of probiotics results in vaginal colonisation (Reid & Bruce 2006). This confirms findings from previous studies which have also shown that oral administration of lactobacilli results in colonisation of the gastrointestinal and the genitourinary tract.

A daily dose of 10^9 viable *Lactobacillus* GR-1 and RC-14 bacteria in 10 women with repeated bacterial vaginosis, yeast infections and/or urinary tract infections (UTIs) resulted in resolution of symptoms in most of the women. Symptoms abated within a fortnight, and all the patients remained healthy for several months following treatment (Reid et al 2001). The same authors reported an enhanced effect of *L. rhamnosus* GR-1 and *L. fermentum* RC-14 administered orally, resulting in rapid vaginal colonisation within 7 days (Reid et al 2001), and even after treatment cessation, there were still some women where this remained to be the case.

Consumption of a yoghurt containing *L. acidophilus* for 1 year by women with recurrent vaginitis resulted in a reduced colonisation by *Candida* infection (Hilton et al 1992).

Other studies have also reported local application or oral ingestion of probiotic lactobacilli and bifidobacteria in vulvovaginitis (Falagas et al 2006) and UTIs (Borchert et al 2008), but there is a need for larger, randomised, controlled, clinical trials to investigate and confirm these effects.

The mechanisms by which *Lactobacillus* spp reduce bacterial vaginosis and UTIs appear to involve antiadhesion factors, byproducts such as hydrogen peroxide and bacteriocins lethal to pathogens and perhaps immune modulation or signalling effects. Bifidobacteria in particular are considered well suited to this activity and have, therefore, been investigated for their effects in the treatment of female genitourinary infections (Korshunov et al 1999).

Additionally, lactobacilli play a significant role in the prevention of UTIs. Studies using intravaginal administration of probiotics such as *Lactobacillus* GR-1 and B-54 or RC-14 strains have demonstrated that treatment resulted in fewer UTIs than placebo and improved the maintenance of normal flora (Reid & Bruce 2006). A significant reduction in UTI rate was also reported in a randomised double-blind study involving 55 premenopausal women (Reid 2001). The study investigated the effectiveness of treatment for 1 year with a weekly suppository containing either 0.5 g *L. rhamnosus* GR-1 and *L. fermentum* B-54 or a *Lactobacillus* growth factor. Treatment resulted in the UTI rate decreasing by 73% and 79%, respectively, with no adverse effects reported.

> ***Clinical note — Dosages tailored to increase probiotic survival***
> Enteric-coated tablets containing probiotics that are gastric acid resistant have been produced (Stadler & Viernstein 2003). More studies, however, are needed to examine the efficacy of these administration forms to deliver and release the probiotic at the appropriate target sites in the gastrointestinal tract.

OTHER USES

Probiotics may have many potentially important clinical applications, and current areas of active research include mostly animal studies investigating a range of diseases including control or prevention of cancer (Fotiadis et al 2008) and prevention or treatment of graft-versus-host disease in transplant recipients (Gerbitz et al 2004).

DOSAGE RANGE

Probiotic doses are usually standardised in terms of the amount of living bacteria per unit of volume. A quality product may contain between 1×10^9 and 1×10^{11} CFU/g; however, the dose required to achieve therapeutic effects varies between strains. If a product contains multiple strains, then each strain should be present at levels of 10^9 to be effective. The viable bacteria are mixed in a suitable matrix, which may contain maltodextrin, amylase and prebiotics such as fructo-oligosaccharides and inulin.

As more information is gathered from probiotic research, it is becoming evident that certain strains or a combination of strains is suitable for different conditions. Different strains of probiotics are chosen and combined to produce specific products for diarrhoea in children, antibiotic induced diarrhoea, travellers' diarrhoea, IBDs etc.

Supplements are best taken with meals to enhance bacterial survival.

A serving of yoghurt containing fewer than 10^8 viable bacteria is unlikely to have any therapeutic activity beyond acting as a nutritional source.

ADVERSE REACTIONS

Probiotics are generally regarded as safe. However, probiotic therapy should be used with caution in the young, elderly and those with immunocompromised function as they may be at increased risk of adverse reactions. Infections, sepsis and meningitis have been reported in adult cases when administered lactobacilli (Land et al 2005, Mackay et al 1999, Rautio et al 1999). Cases of young children and infants have also been reported (Borriello et al 2003).

Oral administration of *S. boulardii* has resulted in fungaemia in 50 patients (Enache-Angoulvant & Hennequin 2005). There is also concern in

critically ill patients because impaired intestinal barrier function could result in infection as a result of bacterial translocation (Land et al 2005, Munoz et al 2005). Recently, there have been reports about increased mortality in patients with severe acute pancreatitis who were administered a multispecies probiotic (Besselink et al 2008).

SIGNIFICANT INTERACTIONS

Antibiotics

Concomitant administration of some strains of probiotics reduces gastrointestinal and genitourinary side effects according to clinical studies — combination can be safely used together and a beneficial interaction is likely.

CONTRAINDICATIONS AND PRECAUTIONS

Specific strains of probiotics are appropriate for different disorders. Probiotics are contraindicated in those people who are hypersensitive to any component of the probiotics-containing product.

PREGNANCY USE

Likely to be safe in pregnancy; however, use of concentrated forms should be supervised by a healthcare professional.

PATIENTS' FAQs

What can probiotics do for me?

Studies have shown that probiotics are beneficial in the treatment of digestive disorders such as diarrhoea and some IBDs and also other conditions not directly connected with the digestive tract, such as vaginal thrush and recurrent cystitis, antibiotic induced and travellers' diarrhoea, IBS, food allergies and eczema.

When will they start to work?

Usually, probiotics can exert beneficial effects in digestive disorders within days although continuous use for several weeks/months may produce long-term benefits and be necessary in the treatment of other disorders.

Are there any safety issues?

Generally, probiotics have a good safety profile; however, high-dose supplements should be used under supervision by the very young, elderly and immunocompromised.

PRACTICE POINTS/PATIENT COUNSELLING

- Although probiotics may improve the long-term bowel flora, probiotic supplementation has many other benefits not associated with direct colonisation of the gastrointestinal tract.
- Studies have shown that probiotics are beneficial in the treatment of digestive disorders such as diarrhoea and some IBDs and also other conditions, such as urogenital infections, antibiotic induced and travellers' diarrhoea, IBS, food allergies, eczema and the prevention and treatment of paediatric AD.
- There is also some evidence that probiotics are essential for both the development and the maintenance of a healthy immune system.
- Probiotics can be administered orally or intravaginally. They can also be taken as yoghurt or other cultured dairy products. It should be noted that only products containing actual probiotic strains will be beneficial. The so-called starter cultures do not necessarily have the same beneficial effects.
- For travellers' diarrhoea, it is recommended that the probiotic dose be started some days before travelling to ensure that the beneficial bacteria have colonised the gut; the dosage may vary depending on the probiotic strain.

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Psyllium

HISTORICAL NOTE Psyllium has a long history of use in both conventional and traditional medical systems and has been listed in various pharmacopoeias around the world.

OTHER NAMES

Psyllium seed, Blonde *Plantaginis ovatae* semen — ripe seeds of *Plantago ovata* (*P. isphagula*).

Plantago ovata semen refers to the unprocessed seed.

White or *blond* psyllium, also known as Indian plantago.

Psyllium seed husk, Blonde *Plantaginis ovatae testa* — referring to the epidermis layers of *Plantago ovata* (*P. isphagula*)

Psyllium seed, Black *Psyllii semen* – referring to the dried ripe seed of *Plantago psyllium* (*P. afra*, *P. arenaria* and *P. indica*)

Black, French or Spanish psyllium comes from *P. psyllium* (syn. *P. afra*) and *P. arenaria* (*P. indica*).

Psyllium seed husk is generally sold over the counter as Metamucil®.

BOTANICAL NAME/FAMILY

Plantago ovata, *P. psyllium*, *P. arenaria* (family Plantago)

PLANT PART USED

Seed coat and seed

CHEMICAL COMPONENTS

Plantago ovata seed husk generally consists of 67–71% fibre, constituents includes 10–30% mucilage (arabinoxylans), iridoid glycosides (≈ aucubin), trace monoterpene alkaloids, sugars, protein, sterols, triterpenes, fatty acids and tannins. Phytosterol and beta-sitosterol (Nakamura et al 2005).

MAIN ACTIONS

Bulking agent

Psyllium husk is commonly used throughout the world as a bulking agent in the treatment of both constipation and diarrhoea. A component of psyllium husk is incompletely fermented, forming a mucilaginous gel which provides lubrication, increases moisture content and facilitates propulsion of the colon contents (Marlett et al 2000).

Psyllium promotes stools that are more frequent and softened, and reduces pain on defecation. Psyllium has been shown to be more beneficial in maintaining regularity than bran (Singh 2007).

Promotes satiety

A placebo-controlled study of a *P. ovata* preparation administered in water found a significant difference in satiety 1 h after consumption (Turnbull & Thomas 1995). Increased satiety was apparent up to 6 h after consumption. A recent animal study showed that amongst its proposed range of action psyllium had the potential to attenuate weight gain (Wang et al 2007).

Lipid lowering

Psyllium husk effectively reduces lipid levels by altering cholesterol metabolism, increasing hepatic cholesterol catabolism and increasing faecal bile acid excretion (Romero et al 2002). *Psyllium* sequesters bile salts during passage through the intestinal lumen as well as physically disrupts the intraluminal formation of micelles, thereby reducing the absorption of cholesterol and re-absorption of bile salts. As a result, bound bile acids are moved to the terminal ileum and colon, thereby interrupting the enterohepatic circulation so that more cholesterol is converted into newly produced bile acids (Rodriguez-Moran et al 1998). It is postulated that this increased hepatic conversion of cholesterol into bile acids results in increased LDL uptake by the liver, leading to decreased levels of serum LDL cholesterol and total cholesterol (Theuwissen & Mensink 2008). Reduced cholesterol biosynthesis results in an upregulation of LDL receptors and enhanced uptake of LDL cholesterol (Shrestha et al 2007). Both the unfermented and viscous components of psyllium are considered responsible for the observed lipid-lowering effects (Marlett & Fischer 2003, Dikeman & Fahey 2006).

Slows glucose absorption

Animal and human models have demonstrated that psyllium modulates the glycaemic response through various mechanisms. Psyllium supplementation delays gastric emptying, small bowel motility and reduces intestinal mixing, thereby slowing and reducing glucose absorption across the intestinal lumen of the small intestine (Dikeman & Fahey 2006). Psyllium has induced an upregulation of GLUT-4 receptors in skeletal muscle cell membranes in vitro (Song et al 2000) and has been shown to improve glycaemic response by modulating postprandial glucose concentrations and insulin

requirements (Anderson et al 1999, Frati-Munari et al 1989, Sierra et al 2001).Wang et al demonstrated in vivo that psyllium enhances insulin sensitivity, reduces weight gain and modulates GLP-1 secretion (Wang et al 2007).

CLINICAL USE

Psyllium is used mainly for its mucilage content, which comes from the seed coat.

Bulking agent

Psyllium is commonly used as a bulking agent to treat constipation or diarrhoea and to regulate stool consistency in people with a colostomy or ileostomy. As a bowel regulator, psyllium husk absorbs water in the colon to increase faecal bulk, which stimulates peristaltic activity. Alternatively, psyllium can be used to promote normal stool formation in people with diarrhoea by decreasing the frequency of fluid stools. Commission E approves the use of black psyllium seed and blond psyllium seed for chronic constipation and when a soft stool is desirable, such as in patients with haemorrhoids, anal fissures or postrectal surgery (Blumenthal et al 2000).

The symptoms associated with constipation-induced haemorrhoids may also be reduced through administration of psyllium. A reduction of pain and length of hospital stay following open haemorrhoidectomy were achieved through supplementation of laxomucil (3.26 g psyllium) (Kecmanovic et al 2004). A subsequent study further identified a reduction of postsurgical tenesmus rate (Kecmanovic et al 2006).

Weight loss aid

Psyllium is used to increase the subjective feeling of satiety before and between meals in an attempt to reduce total caloric intake. One study comparing *Plantago ovata* preparation (20 g granules with 200 mL water) to water or a placebo preparation found a significant difference in fullness 1 h after consumption (Turnbull & Thomas 1995). Other studies have confirmed a suppressant effect on hunger and increased satiety that remains apparent up to 6 h after consumption. Psyllium also significantly delays gastric emptying from the third hour after a meal (Bergmann et al 1992, Delargy et al 1997).

Hyperlipidaemia

Psyllium is also used as a cholesterol-lowering agent, usually as an adjunct to a low-fat diet (Reid et al 2002). Soluble fibres, such as psyllium husk, increase the cholesterol-lowering effect of a low-fat diet in people with elevated cholesterol (Anderson et al 2000). A meta-analysis of 21 controlled clinical trials (n = 1697) testing psyllium dosages ranging between 3.0 and 20.4 g daily confirmed that psyllium produced a time- and dose-dependent serum cholesterol-lowering effect in patients with mild-to-moderate hypercholesterolaemia (Wei et al 2009). Reductions in serum cholesterol occurred more quickly than changes in LDL cholesterol with psyllium supplementation.

Similar results were obtained in two previously published meta-analyses. Davidson et al (1996) evaluated data from eight studies and found that psyllium (10.2 g/day) lowered serum total cholesterol by 4%, LDL cholesterol by 7% and the ratio of apolipoprotein (apo) B to apo A–I by 6% relative to placebo. This was achieved together with a low-fat diet over 8 weeks. It has also been used with some success in the paediatric population and is easy to incorporate into various foods (Davidson et al 1996). Olson et al (1997), using the data from 404 subjects with mild-to-moderate hypercholesterolaemia concomitantly consuming a high-fat diet supplemented with psyllium in the form of cereal, found psyllium to be beneficial in lowering both LDL and total cholesterols; however, HDL concentrations were unaffected (Olson et al 1997).

Studies with statin drugs

A 12-week blinded, placebo-controlled study comprising 68 patients demonstrated that supplementation of dietary psyllium 15 g (Metamucil®) daily in patients taking 10 mg of simvastatin was as effective in lowering cholesterol as 20 mg of simvastatin alone (Moreyra et al 2005). However, a 4-week open label, randomised, parallel study of 36 subjects demonstrated that 10 g of psyllium daily added to 20 mg of lovastatin provided an additive effect in cholesterol lowering than lovastatin alone, although the difference was not statistically significant (Agrawal et al 2007). The duration of the supplementation may offer some insight into conflicting outcomes. In a 12-week study involving 100 subjects with hyperlipidaemia randomised to receive either a combination of isapgol powder (Naturolax) 5.6 g twice daily and atorvastatin 10 mg once daily or atorvastatin 10 mg daily alone, significant reduction in LDL cholesterol was achieved at the end of week 8; there was, however, no difference between treatment groups. However, at the end of week 12, the combination of isapgol and atorvastatin produced significantly greater reduction in LDL when compared to atorvastatin alone (Jayaram et al 2007).

Diabetes

Fibre products, such as psyllium, have been used as an aid to metabolic control in patients with diabetes (Pittler & Ernst 2004, Sierra et al 2002). Epidemiological and clinical data suggest a role for both soluble and insoluble fibre products in the management of hyperglycaemia. It appears that soluble fibre has a dose-dependent effect on serum glucose levels and the insulin response to a meal, improves glycaemic control in type 2 diabetes and can reduce the amount of medication required (Pastors et al 1991).

The adjunct use of 5.1 g psyllium twice daily for 8 weeks with a traditional diet for 34 men with type 2 diabetes and mild-to-moderate hypercholesterolaemia was well tolerated and shown to improve glycaemic and lipid levels as compared to placebo (Anderson et al 1999). One clinical study using 14 g/day of psyllium (Plantaben, ALTANA Pharma, Mexico) showed a significant 12.2% reduction in glucose absorption, as well as a significant reduction

in total cholesterol and LDL cholesterol, and also uric acid (Sierra et al 2002). Another study identified that a higher dose (20 g/day in divided doses) may produce better results and significantly lowers both basal and postprandial hyperglycaemia (Frati-Munari et al 1989). In an 8-week double-blind, placebo-controlled study of 49 subjects, psyllium (5.1 g twice daily) was evaluated as an adjunct to the use of diet and pharmaceutical hypoglycaemic therapy in patients with type 2 diabetes. Fasting blood glucose and glycosylated haemoglobin were significantly reduced following psyllium administration and improved gastric tolerance to metformin was identified in the psyllium group. The authors concluded psyllium to be safe, well tolerated and improved glycaemic control in patients with type 2 diabetes (Ziai et al 2005). Psyllium significantly improved the breakfast postprandial glycaemic, insulinemic and free fatty acid response in 45 patients with type 2 diabetes mellitus participating in a randomised, crossover intervention trial of a low-glycaemic load breakfast meal containing soluble psyllium fibre 6.6 g for 3 weeks duration (Clark et al 2006).

Irritable bowel syndrome (IBS)

In IBS with constipation predominant symptoms, soluble fibres, including psyllium, have been found to be more effective than insoluble fibres in relieving symptoms and reducing constipation (Chang et al 2006); however, fibre is not considered to be effective in improving abdominal pain, bloating or distension (Fernandez-Banares 1999). Black and blond psyllium seed is approved for use by Commission E in IBS and recommended when a soft stool is desired (Blumenthal et al 2000).

Inflammatory bowel disease

A limited number of studies have examined the ability of psyllium to maintain remission in ulcerative colitis. A randomised controlled trial of 120 patients with ulcerative colitis demonstrated that patients receiving treatment with a symbiotic therapy of *Bifidobacterium longum* (2×10^9 colony-forming units, 1 daily) and psyllium (8 g daily) reported greater 'quality-of-life' changes than those treated with probiotic or psyllium alone (Fujimori et al 2009).

Hypertension

Participants in a randomised controlled trial of 41 hypertensive patients increased their intake of dietary protein and psyllium (additional 12 g/day) for 8 weeks. A net reduction in 24-h systolic blood pressure of 5.9 mmHg was demonstrated (Burke et al 2001). In a 6-month, randomised, open-label clinical trial involving 141 hypertensive and overweight patients, treatment with psyllium powder as compared to guar gum appeared to significantly reduce systolic and diastolic blood pressures (Cicero et al 2007).

OTHER USES

In the confectionery industry, it is used as a thickening agent in ice cream and frozen desserts.

DOSAGE RANGE

General recommendations

- Blond psyllium seed: 12–40 g of whole seeds or equivalent taken in divided doses daily.
- Black psyllium seed: 10–30 g of whole or ground seeds or equivalent taken in divided doses daily.

Seeds should be presoaked in 100–150 mL of warm water for several hours before ingestion. Each dose should be followed by another full glass of water.

- Powdered blond psyllium seed husk: 4–5 g taken up to four times daily. Stir desired dose into 150 mL of water and drink immediately. Follow each dose with ½–1 glass of water.

According to clinical studies

- Weight loss: *Plantago ovata* preparation (20 g granules with 200 mL water).
- Constipation: 7–11 g daily in divided doses with water.
- Hyperlipidaemia: 7–20 g daily in divided doses with water.
- Hyperglycaemia: 10–15 g daily in divided doses with water.
- Diabetes: 14–20 g daily in divided doses.
- Diarrhoea: 7–30 g in divided doses for 7 days with water.
- Haemorrhoids: 7 g daily for 6 weeks with water.
- Children 6–12 years: 3–8 g in divided doses.

SIGNIFICANT INTERACTIONS

Calcium

Animal studies suggest that soluble fibre from sources of purified psyllium negatively impact calcium balance by decreasing the bioavailability of calcium from the diet (Luccia & Kunkel 2002) — psyllium and other soluble fibre supplements should be taken at least 1 h before or after calcium.

Lithium

Soluble fibre may decrease the bioavailability of lithium (EMEA 2003) — take psyllium at least 1 h before or after lithium.

Coumarin derivatives

Soluble fibre may decrease the bioavailability of coumarin derivatives (EMEA 2003) — take psyllium at least 1 h before or after coumarin derivatives.

Vitamin B_{12}

Soluble fibre may decrease the bioavailability of vitamin B_{12} (EMEA 2003) — take psyllium at least 1 h before or after vitamin B_{12}.

Cardiac glycosides

Soluble fibre may decrease the bioavailability of cardiac glycosides (EMEA 2003) — take psyllium at least 1 h before or after cardiac glycosides.

Hypoglycaemic agents

Additive hypoglycaemic effects are theoretically possible — drug dose may need modification and

the outcome can be favourable under professional supervision.

Anticonvulsant medication
Absorption concomitantly administered with psyllium may be delayed (EMEA 2007) — product taken one hour to half an hour before or after the medicinal product.

Thyroid hormones
Medication dose may need to be adjusted — seek medical supervision (EMEA 2007).

Lipid lowering agents
Concomitant use of psyllium with lipid-lowering drugs may lead to a reduction in drug dose and further lipid-lowering effects — beneficial interaction.

ADVERSE REACTIONS
Allergy is possible, although rare and is characterised by tightness in the chest, wheezing and urticaria. According to a study of healthcare workers, daily exposure to laxatives containing plantago ovata causes sensitisation to plantago ovata seed in approximately 14% of people (Bernedo et al 2008). Psyllium should not be consumed dry, as it may cause oesophageal obstruction. In practice, it is not unusual for people to experience flatulence, bloating and mild abdominal discomfort when they start to use psyllium; however, these symptoms can reduce with long-term use.

CONTRAINDICATIONS AND PRECAUTIONS
Although psyllium is considered a safe substance, it should not be used by people with partial or complete bowel obstruction, colonic impaction or stenosis of the gastrointestinal tract.

According to Commission E, blond psyllium seed is contraindicated if there is difficulty regulating diabetes mellitus.

PREGNANCY USE
May be used during pregnancy and lactation.

PRACTICE POINTS/PATIENT COUNSELLING
- Psyllium seed husk is a water-soluble fibre that forms a mucilaginous gel on contact with aqueous fluids and is degraded by human intestinal flora.
- It is most commonly used to treat constipation or diarrhoea and to regulate stool consistency.
- It is also used to promote satiety and weight loss, and as an aid to metabolic control in diabetes and hyperlipidaemia when combined with a low-fat diet.
- The seeds should be presoaked in warm water for several hours before ingestion and each dose should be followed by a full glass of water. Ingesting it dry may cause oesophageal obstruction.
- Although generally safe, it should not be used by people with partial or complete bowel obstruction, colonic impaction or stenosis of the gastrointestinal tract.

PATIENTS' FAQs
What will this herb do for me?
Psyllium is a bulking agent that can regulate stool consistency, increase satiety, improve metabolic control in diabetes and reduce cholesterol when combined with a low-fat diet.

When will it start to work?
As a bulking agent, it will start to have an effect within several hours. It will improve satiety within 30–60 min and has a mild cholesterol-lowering effect after 8 weeks of use.

Are there any safety issues?
Although generally safe, it should not be ingested dry or used by people with partial or complete bowel obstruction, colonic impaction or stenosis of the gastrointestinal tract.

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Pygeum

HISTORICAL NOTE *Pygeum africanum* is a large, evergreen tree native to Africa. Its bark has been used medicinally for thousands of years by traditional African healers to treat bladder disorders, kidney disease, prostate disorders and malaria, as well as male baldness and to enhance sexual functioning. Since the late 1960s, the extract has been used in clinical practice in Europe; however, because of overharvesting, the plant is now considered an endangered species and efforts are underway to protect it.

COMMON NAME
Pygeum

OTHER NAMES
African plum tree, African prune tree, *Pygeum africanum*, alumty, iluo, kirah, Natal tree, Pignil®, Pronitol®, Tanaden®

BOTANICAL NAME/FAMILY
Prunus africana (Hook. f.) KalRm (family Rosaceae)

PLANT PART USED
Bark

CHEMICAL COMPONENTS
Phytosterols (beta-sitosterol, beta-sitostenone), pentacyclic triterpenes (oleanolic and ursolic acids) and ferulic esters (*n*-docosanol and *n*-tetracosanol) (Stewart 2003) and atraric acid and benzoic acid (Schleich et al 2006).

Clinical note — Popular to the point of extinction?
For the past 35 years, pygeum has been used in Europe for the treatment of benign prostatic hyperplasia (BPH) and other disorders. The bark is entirely wild collected, mainly from Cameroon, Madagascar, Equatorial Guinea and Kenya, and exported principally to Europe for production into commercial medicinal extracts (Stewart 2003). Since 1995, it has been considered an endangered species, so attempts at cultivation are underway to protect the plant from extinction. Prior to 1966 when it was discovered to have significant medicinal effects, *P. africana* was a relatively common but never abundant species. The reasons for its demise include economic, social and ecological factors. Currently, wildcrafting is no longer commercially viable in Cameroon, and harvest has ceased in both Uganda and Kenya.

MAIN ACTIONS

Pygeum has demonstrated several different pharmacological effects according to in-vitro and in-vivo data. The majority of initial studies conducted on *P. africanum* were investigating its role in the symptomatic relief of BPH. More recent research is seeking to elucidate pygeum's pharmacological capacity in the modulation and restoration of bladder function, androgen receptor modification and attenuating prostatic cancer cell line replication.

Hormonal effects

In-vivo studies have shown that orally administered pygeum extract has a significant effect on dihydrotestosterone (DHT)-induced prostatic enlargement (Choo et al 2000, Yoshimura et al 2003). Pretreatment with pygeum extract counteracted the effect of DHT-induced prostate enlargement (Choo et al 2000), and the more recent study found that oral administration of pygeum extract suppressed the effects of DHT on micturition (Yoshimura et al 2003) and effectively suppressed prostatic growth when coadministered with DHT; however, it did not reverse established prostatic growth when administered after DHT. A comparative study found that pygeum exerted only a weak inhibition of 5-alpha reductase compared to that of finasteride (Rhodes et al 1993). Phyto-oestrogens isolated in pygeum can exert a dose-dependent oestrogenic or anti-oestrogenic effect, according to other in-vivo tests (Mathe et al 1995), and may also contribute to its effects in the prostate.

Antiandrogenic

Recent in-vitro investigations have confirmed the antiandrogenic activity of pygeum. When compared to *Serenoa repens* and *Cucurbita pepo*, pygeum exhibited the highest androgen antagonistic activity (Schleich et al 2006). Atraric acid, isolated from pygeum, has been shown to selectively inhibit transactivation-mediated ligand-activated human androgen receptor, inhibiting the expression of endogenous prostate-specific antigen (Schleich et al 2006).

Anti-inflammatory

Phytosterols (beta-sitosterol, beta-sitostenone) reportedly inhibit the production of prostaglandins in the prostate, which suppresses the inflammatory symptoms associated with BPH and chronic prostatitis. The pentacyclic triterpenes (oleanolic and ursolic acids) are believed to inhibit the activity of glucosyltransferase, an enzyme involved in the inflammation process (Stewart 2003).

Studies with pygeum extract confirm that it decreases production of leukotrienes and other 5-lipoxygenase metabolites (Cristoni et al 2000).

Bladder effects

Pygeum protects the bladder from contractile dysfunction induced by ischaemia and reperfusion according to in-vivo animal studies (Chen et al 1999). Pretreatment with pygeum prior to induced partial outlet obstruction in animal models prevents the development of contractile dysfunction, possibly by protecting the bladder from ischaemic injury (Levin et al 2005). Administration of pygeum was found to reverse already ischaemic compromised bladder function in a dose-dependent manner (Levin et al 2002).

Inhibition of fibroblast proliferation

Pygeum is a potent inhibitor of prostatic growth factor-mediated fibroblast proliferation, as demonstrated in animal models (Yablonsky et al 1997, Szolnoki et al 2001). A dose-dependent inhibition of fibroblastic growth was exerted in human stromal cells treated with pygeum extract (Boulbes et al 2006).

Chemopreventative

Recent investigations have focused primarily upon *P. africanum* regulation of cancer cell growth in vitro and in vivo. Treatment with pygeum extract exhibited a significant and dose-dependent inhibition of human prostate cancer cell lines and BPH-derived epithelial cells. Pygeum also exerted a potent antimitogenic action in this study (Santa Maria Margalef et al 2003). Pygeum-treated mice displayed a significant reduction in prostate cancer incidence (35%) in comparison to the casein-fed mice (62.5%) (Shenouda et al 2007).

OTHER ACTIONS

Ferulic esters (*n*-docosanol and *n*-tetracosanol) reportedly lower blood levels of cholesterol, from which testosterone is produced (Stewart 2003).

CLINICAL USE

The most commonly investigated form of *P. africanum* is Tanenan® (DEBAT pharmaceuticals, France), which is a lipophilic extract standardised to contain 13% total plant sterols. One capsule of Tadenan® contains 50 mg of standardised extract.

Benign prostatic hyperplasia (BPH)

Clinical trials since the late 1970s have been encouraging, most reporting improvement in BPH symptoms.

A Cochrane systematic review analysed the results of 18 clinical trials that involved a total of 1562 participants (Wilt et al 2002). Seventeen studies were double blinded, and the mean treatment duration was 61 ± 21 days (range 30–122 days). Most studies used a standardised extract of *P. africanum* in doses ranging from 75 to 200 mg/day.

The overall summary effect size indicated a large and statistically significant improvement with *P. africanum*. More specifically, active treatment increased peak urine flow by 23% and reduced residual urine volume by 24%, and physicians were twice as likely to report that their patients were experiencing an overall improvement in symptoms when pygeum was being used. The authors report that these findings are similar to other widely used treatment options and that treatment was well tolerated.

It is believed that the phytosterols, pentacyclic triterpenes and ferulic esters found within the extract work synergistically to counteract the structural and biochemical changes associated with BPH.

A systematic review of clinical trials for the use of phytotherapy in the treatment of lower urinary tract symptoms secondary to BPH concluded that pygeum improved flow rates and symptoms compared to placebo (Dedhia & McVary 2008). A prior critical review of pygeum highlighted the difficulty in establishing concise clinical efficacy of pygeum in BPH owing to poorly designed trials of limited duration and high placebo response. Researchers suggested the need for large-scale clinical trials (Edgar et al 2007).

OTHER USES

Fertility disorders

Pygeum extract was used experimentally in the treatment of 22 men with reduced fertility and diminished prostatic secretion and proved to have a beneficial effect (Lucchetta et al 1984). Treatment was administered every day over 2 months and was most effective in men who did not have prostatitis.

DOSAGE RANGE

According to clinical studies

- BPH: 50–100 mg of extract twice daily standardised to 12–13% total sterols

ADVERSE REACTIONS

Pygeum is well tolerated with side effects similar to placebo (Wilt et al 2002). Mild gastrointestinal discomfort has been reported.

SIGNIFICANT INTERACTIONS

None known.

CONTRAINDICATIONS AND PRECAUTIONS

People with known allergies should avoid use.

PREGNANCY USE

Safety not scientifically established; however, it is not used for any indication that would cause a pregnant woman to use it.

PRACTICE POINTS/PATIENT COUNSELLING

- Pygeum is a popular treatment in Europe for BPH.
- A systematic review of 18 clinical studies found that it has significant effects in BPH such as increasing peak urine, reducing residual urine volume and producing an overall improvement in symptoms.
- Several different mechanisms of action have been identified using animal models, which would explain its effectiveness in BPH.
- According to clinical studies, the dose used is 50–100 mg of standardised extract twice daily for BPH and the treatment is well tolerated.
- Overharvesting has meant the tree is now considered endangered and efforts are being made to protect it from extinction.

PATIENTS' FAQs

What will this herb do for me?

Standardised pygeum extract is an effective treatment in benign prostate enlargement or inflammation and improves several symptoms.

When will it start to work?

Some men will notice an improvement in symptoms after 4 weeks; however, others will require a long-term treatment.

Are there any safety issues?

It is a well-tolerated treatment but should not be used by people with a known allergy to the plant. If symptoms worsen, seek professional advice.

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Quercetin

BACKGROUND AND RELEVANT PHARMACOKINETICS

Quercetin is a flavonol belonging to a group of polyphenolic substances known as flavonoids or bioflavonoids. The first flavonoids were identified in 1936 by Albert Szent-Györgyi, who was awarded the Nobel Prize for his discovery of vitamin C (Challem 1998).

Studies on the absorption, bioavailability and metabolism of quercetin after oral intake in humans have produced contradictory results (Graefe et al 1999). The nature of quercetin metabolites in plasma is currently unclear and requires further elucidation (Day & Williamson 2001), which may in part explain these inconsistencies.

In recent human trials, supplementation increased plasma quercetin concentrations in a dose-dependent manner: 178% (50 mg), 359% (100 mg) and 570% (150 mg); and maximum plasma concentrations were reached 6 h after intake of a 150-mg dose. There was also a significant variation between individuals for plasma quercetin concentrations (36–57%) (Egert et al 2008). Factors that may improve bioavailability include gender (especially females taking oral contraceptives), gastrointestinal flora (Erlund 2004) and concurrent intake of bromelain and papain (Shoskes et al 1999). Absorption from onions is three times that of apples (Hollman et al 1997) and twice that of black tea (deVries et al 1998).

The main determinant for the absorption of quercetin conjugates is the nature of the sugar moiety. Glucose-bound glycosides (quercetin glucosides) are effectively absorbed from the small intestine because the cells possess glucoside-hydrolysing activity and their glucose transport system is capable of participating in glucoside absorption, whereas quercetin glycosides are subject to deglycosidation by enterobacteria before absorption in the large intestine (Murota & Terao 2003).

After absorption, quercetin is transported to the liver via the portal circulation, where it undergoes significant first-pass metabolism. Peak plasma levels of quercetin occur from 0.7 to 9 h following ingestion, and the elimination half-life of quercetin is approximately 23–28 h (Hollman et al 1997, PDRHealth 2005). Due to its long half-life, repeated consumption of quercetin-containing foods should cause accumulation of quercetin in the body. Excretion is likely to be via the biliary system (Erlund 2004).

CHEMICAL COMPONENTS

Quercetin, also known as meletin and sophretin, is known chemically as 2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy-4H-1-benzopyran-4-one and 3,3′,4′5,7-penthydroxyflavone. It is typically found in plants as a glycone or carbohydrate conjugate but does not in itself possess a carbohydrate moiety in its structure. Quercetin glycone conjugates include rutin (quercetin-3-rutinoside) and quercitrin (thujin, quercetin-3-L-rhamnoside or 3-rhamnosylquercetin) (Erlund et al 2000, PDRHealth 2005).

FOOD SOURCES

Apples, berries (blackcurrants, lingonberries and bilberries), beans, black tea, broccoli, grapes, green tea, onions and red wine (Somerset & Johannot 2008)

Herbal medicines such as St John's wort, *Ginkgo biloba*, *Vaccinium macrocarpon* (cranberry) and *Oenothera biennis* (evening primrose) also contain quercetin and this may help to explain some of their therapeutic benefits.

MAIN ACTIONS

Antioxidant/pro-oxidant

Quercetin is a phenolic antioxidant and has been shown to inhibit lipid peroxidation, protecting the lens of the eye (Cornish et al 2002) and renal tubular epithelial cells from oxidant-induced injury (Pietruck et al 2003). The antioxidant activity may be the result of free radical scavenging, metal chelation, enzyme inhibition or the induction of protective enzymes (Erlund 2004). In addition, while quercetin does not appear to significantly affect the elevation of intracellular calcium concentration that results from oxidative stress, it does appear to greatly delay the process of calcium-dependent cell death that usually follows (Sakanashi et al 2008).

While some studies demonstrate that quercetin treatment at low concentrations or for short periods may exert an antioxidant effect, other trials suggest that higher concentrations or long-term treatment may produce a pro-oxidant effect (Robaszkiewicz et al 2007, Ferraresi et al 2005). These effects may be due to induction of oxidative stress due to formation of reactive oxygen species in the extracellular medium (Robaszkiewicz et al 2007) or increasing oxidant activity due to a reduction in glutathione (GSH) levels (Ferraresi et al 2005). The paradox is that in the process of offering protection, quercetin depletes GSH levels and is converted into potentially toxic products (thiol-reactive quercetin metabolites) (Boots et al 2007). In the absence of GSH, potentially harmful oxidation products such as orthoquinone may be produced when quercetin exerts its antioxidant activity. Therefore, adequate GSH levels should be maintained when quercetin is supplemented (Boots et al 2003).

In recent human trials, while daily supplementation of quercetin (50, 100 and 150 mg/day) for 2 weeks dose-dependently increased plasma quercetin concentrations, it did not appear to affect antioxidant status, oxidised low density lipoprotein (LDL), inflammation or metabolism (Egert et al 2008). Furthermore, in a placebo-controlled

trial of 40 athletes, chronic quercetin ingestion (1000 mg/day) for 6 weeks was not able to exert protection from exercise-induced oxidative stress and inflammation (McAnulty et al 2008).

Anti-inflammatory

In animal and in-vitro studies, quercetin inhibits inflammation by modulating neutrophil function, prostanoid synthesis, cytokine production and iNOS expression via the inhibition of the neutrophil factor (NF)-kappa-B pathway (Busse et al 1984, Comalada et al 2005, Morikawa et al 2003). While quercetin supplementation has been shown to decrease circulating markers of inflammation in mice (Stewart et al 2008), these effects have not been replicated in humans (Egert et al 2008, McAnulty et al 2008).

Antiviral

Quercetin causes a dose-dependent reduction in the infectivity and intracellular replication of herpes simplex virus (HSV)-1, poliovirus type 1, parainfluenza virus type 3 and respiratory syncytial virus in vitro (Kaul et al 1985); however, pretreatment with quercetin does not appear to provide any additional benefit. Animal studies have also suggested that the antioxidant effects of quercetin may protect the lungs from the deleterious effects of oxygen-derived free radicals released during influenza infection (Kumar et al 2005).

Immunomodulation

Results from animal and in-vitro studies have produced contradictory results, suggesting both an induction and an inhibition of Th1 cytokines (Muthian & Bright 2004, Nair et al 2002).

According to in-vitro data, quercetin induces Th1-derived cytokines (promoting cellular immunity) and inhibits Th2-derived cytokines, which exert negative effects on cellular immunity (Nair et al 2002). An excess of Th2 cytokines has also been implicated in allergic tendencies, which provides a theoretical basis for the use of quercetin as an anti-allergic substance. Conversely, animal studies have demonstrated that quercetin is able to inhibit Th1 differentiation and signalling of IL-12 (Muthian & Bright 2004) and appears to exert an effect on Th1-mediated immune responses through suppression of both IFNgamma and IL-2 cytokine production (Yu et al 2008). As a result, a possibility exists that quercetin actually exerts an immunomodulatory effect on these cells.

In mice, a short-term quercetin supplementation (12.5 mg/kg administered via gavage) for 7 days before viral challenge reduced the impact of stressful exercise on susceptibility to respiratory infection (Davis et al 2008). This effect was replicated in a human trial of 40 trained male cyclists receiving 1000 mg/day of quercetin or placebo for 2 weeks. Upper respiratory tract infection (URTI) incidence differed significantly between groups during the 2-week postexercise period (quercetin = 1/20 vs placebo = 9/20, $P = 0.004$), despite there being no significant differences in immune function tests (Nieman et al 2007).

Anti-allergy

Quercetin is structurally similar to the anti-allergic drug disodium cromoglycate (cromolyn) and has been proposed as a useful treatment for mast cell-derived allergic inflammatory diseases (Min et al 2007). Anti-asthmatic activity similar to cromolyn sodium and dexamethasone has been demonstrated in guinea pigs (Moon et al 2008).

In-vitro and animal studies demonstrate that quercetin stabilises mast cells, neutrophils and basophils inhibiting antigen as well as mitogen-induced histamine release (Blackburn et al 1987, Busse et al 1984, Middleton & Drzewiecki 1982, Middleton et al 1981, Ogasawara et al 1996, Pearce et al 1984). Inhibition of inflammatory enzymes, prostaglandins and leukotrienes, and modulation of Th2 excess may further contribute to the anti-allergic effects. Pretreatment with quercetin does not appear to produce any additional benefits.

Antihypertensive

Chronic treatment with quercetin lowers blood pressure and restores endothelial dysfunction in animal models of hypertension (Garcia-Saura et al 2005, Sanchez et al 2006). This effect may be in part due to modulation of renal function including increased urinary and sodium output (Mackraj et al 2008).

In a small randomised, double-blind, placebo-controlled, crossover study, 730 mg quercetin/day for 4 weeks resulted in reductions in mean systolic (-7 ± 2 mmHg), diastolic (-5 ± 2 mmHg) and arterial blood pressures (-5 ± 2 mmHg) ($P < 0.01$) in patients with stage 1 hypertension. Significant effects were not demonstrated in prehypertensive subjects, and indices of oxidant stress were not affected by quercetin (Edwards et al 2007).

Cardioprotective

During inflammation, circulating conjugates of quercetin pass through the endothelium to reach vascular smooth muscle cells where they exert their biological effects and are then deconjugated (Mochizuki et al 2004).

The cardioprotective effects of quercetin may be related to its vasorelaxant (Ke Chen & Pace-Asciak 1996, Roghani et al 2004), anti-inflammatory and antioxidant properties and inhibition of vascular smooth muscle cell proliferation and migration (Alcocer et al 2002, Moon et al 2003) as demonstrated in animal and in-vitro models.

Animal experiments indicate that doses of quercetin equivalent to one to two glasses of red wine exert a cardioprotective effect following ischaemia–reperfusion by improving the function of mitochondria, which play a critical role in myocardial recovery (Brookes et al 2002), and may also prevent the development of atherosclerosis through several indirect mechanisms (Auger et al 2005). Quercetin has demonstrated a protective effect against adriamycin-induced cardiotoxicity in mice. The effect is likely to be related to enhanced myocardial superoxide dismutase (SOD) activity, decreased iNOS activity and inhibition of myocardial apoptosis (Pei et al 2007). In humans, quercetin inhibits platelet

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aggregation and signalling and thrombus formation at a dose of 150 or 300 mg quercetin-4′-O-beta-D-glucoside (Hubbard et al 2004). This effect, however, may not occur with clinically relevant doses.

Anti-atherogenic

Adhesion of circulating monocytes to vascular endothelial cells is a critical step in both inflammation and atherosclerosis. Experimental studies have indicated that both quercetin and its metabolites can inhibit the expression of key molecules involved in monocyte recruitment during the early stages of atherosclerosis (Tribolo et al 2008), suggesting a theoretical basis for the use of quercetin in the prevention of this condition. Further human trials are required to examine this effect.

Neuroprotective

Quercetin protects neuronal cells from oxidative stress-induced neurotoxicity (Heo & Lee 2004) and inflammatory-related neuronal injury (Chen et al 2005). At lower doses, it has been proposed as a treatment for Alzheimer's disease and other oxidative stress-related neurodegenerative diseases; however, higher doses may be neurotoxic (Ansari et al 2008).

Cognitive enhancement

Anxiolytic effects have been demonstrated in stress-affected mice (Kumar & Goyal 2008) and both anxiolytic and cognitive enhancing effects in rats following quercetin treatment (Priprem et al 2008).

Gastroprotective

Quercetin treatment (100 mg/kg/day by intragastric gavage) inhibits hyperproliferation of gastric mucosal cells in rats treated with chronic oral ethanol (Liu et al 2008). It has been suggested that the gastroprotective effect of quercetin in animal models may be due to its antiperoxidative, antioxidant and antihistamine effects, resulting in a significant reduction in the number of mast cells and size of gastric erosions (Kahraman et al 2003).

Hepatoprotective

In-vitro and animal studies have demonstrated the hepatoprotective effects of quercetin. It protects the liver from oxidative damage and may reduce biliary obstruction (Alia et al 2006, Peres et al 2000). In experimental models, quercetin protects human hepatocytes from ethanol-induced oxidative stress (Yao et al 2007) and reduces liver fibrosis in rats by enhancing antioxidant enzyme activity (Amalia et al 2007). Pretreatment of rats with quercetin (10 mg/kg) reduced the mortality rate for paracetamol (1 g/kg) from 100 to 30% and prevented liver damage at sublethal doses (640 mg/kg) (Janbaz et al 2004).

Chemoprotective

In the 1970s, quercetin was considered to be carcinogenic after demonstrating mutagenicity in the Ames test; however, subsequent long-term studies have refuted this and demonstrated an anticarcinogenic effect in laboratory animals (Erlund 2004). Epidemiological and experimental studies have demonstrated potential benefits for melanoma (Thangasamy et al 2007), colon, lung (Murakami et al 2008), breast (Lin et al 2008) and liver cancer (Mu et al 2007). Further research is warranted.

In-vitro and preliminary animal and human data indicate that quercetin inhibits tumour growth and induces apoptosis. The anticarcinogenic effects may be due to its antioxidant properties, protection against DNA damage, inhibition of angiogenesis, effects on gene expression, effects on cell cycle regulation, phyto-oestrogen-like activity, interaction with type II oestrogen binding sites and tyrosine kinase inhibition (Zhang et al 2008, Duraj et al 2005, Erlund 2004, Igura et al 2001, Lamson & Brignall 2000, Lee et al 2003, 2005, Tan et al 2003, van der Woude et al 2005, Wilms et al 2005). Quercetin may also protect against nicotine-induced cellular and DNA damage in rats by modulating lipid peroxidation and augmenting antioxidant defence systems (Muthukumaran et al 2008a, 2008b). Radioprotective effects have also been reported (Devipriya et al 2008).

Antidiabetic effects

Oral administration of quercetin (10 mg/kg body weight) to diabetic rats restores vascular function, and this is thought to be due to enhancement in the bioavailability of endothelium-derived nitric oxide as well as a reduction in blood glucose levels and oxidative stress (Machha et al 2007). Diabetic rats receiving quercetin (15 mg/kg/day) for 4 weeks also experienced a decrease in blood glucose and an increase in plasma insulin, calcium and magnesium (Kanter et al 2007). In addition, quercetin has been shown to inhibit human lens aldose reductase by 50% in vitro (Chaudhry et al 1983) and may be responsible for the reduction in cataract formation observed in diabetic rats receiving either dietary or topical quercetin (Beyer-Mears & Farnsworth 1979).

Preventing bone loss

In rabbits, the addition of quercetin to a collagen matrix has been shown to increase new bone formation (Wong & Rabie 2008). Quercetin is claimed to play an important role in preventing bone loss by affecting osteoclastogenesis and regulating many systemic and local factors, including hormones and cytokines (Son et al 2006), providing a theoretical basis for its use in the prevention of postmenopausal bone loss. In-vitro studies demonstrate that bone resorption is mediated by oestrogen receptor proteins through the inhibition of receptor activator of nuclear factor kappa beta (RANK) protein or the activation of caspases (Rassi et al 2005, Wattel et al 2003). However, in-vitro studies also suggest that quercetin inhibits the metabolism of not only osteoclasts (bone resorption cells) but also osteoblasts (bone-forming cells), and therefore, further research is required to elucidate whether quercetin increases or decreases bone mass in vivo (Notoya et al 2004).

Sperm quality

High doses of quercetin delivered by injection to rats resulted in improved sperm motility, viability and concentration and increased the weight of the

testes, epididymis and vas deferens (Taepongsorat et al 2008). Oral administration of quercetin and onions (containing quercetin) to mice has also been shown to reduce the male reproductive toxicity (sperm abnormalities) induced by diesel exhaust particles (Izawa et al 2008). The potential significance of these results to humans is unclear.

OTHER ACTIONS

Quercetin has been shown to reduce oxalate-induced urinary crystal formation and increase catalase and SOD activities in rats (Park et al 2008).

CLINICAL USE

Allergies

Quercetin is used in the treatment of acute and chronic allergic symptoms, such as hayfever and chronic rhinitis. The anti-inflammatory activity of quercetin and its ability to block substances involved in allergies provide a rationale for its use in these indications. Quercetin stabilises mast cells, neutrophils and basophils and inhibits histamine release (Blackburn et al 1987, Busse et al 1984, Middleton & Drzewiecki 1982, Middleton et al 1981, Ogasawara et al 1996, Pearce et al 1984). It acts as an inhibitor of mast cell secretion; reduces the release of tryptase, monocyte chemotactic protein-1 (MCP-1) and IL-6 and down-regulates histidine decarboxylase mRNA from several mast cell lines (Shaik et al 2006).

In a study of 123 patients sensitised to house dust mite and displaying nasal symptoms of mild to severe perennial allergic rhinitis (Otsuka et al 1995), nasal scrapings were taken and histamine release measured as a percentage of the total content in the specimen. Antigen exposure resulted in an increase in mast cells of the epithelial layer of the nasal mucosa, resulting in nasal hypersensitivity. Quercetin inhibited histamine release by 46–96% in a dose-dependent manner.

Large-scale human trials are required to fully elucidate the potential for quercetin to inhibit allergic symptoms caused by the release of histamine.

Asthma

Quercetin has also been used as an adjunct in the management of asthma, often in combination with vitamin C because of its anti-allergic activity and ability to inhibit leukotriene synthesis (Formica & Regelson 1995). Controlled studies are still required to determine its effectiveness.

Preventing diabetic complications

As quercetin has been shown to inhibit aldose reductase, the first enzyme in the polyol pathway, a theoretical basis exists for its use in the prevention of long-term diabetic complications such as cataracts, nephropathy, retinopathy and neuropathy (Chaudhry et al 1983). Quercetin may also provide beneficial effects in people with diabetes by decreasing oxidative stress and preserving pancreatic beta-cell integrity (Coskun et al 2005).

Preliminary evidence suggests a possible antinociceptive activity of quercetin, probably through modulation of opioidergic mechanism, suggesting a potential for the treatment of diabetic neuropathic pain (Anjaneyulu & Chopra 2003). Topical application of quercetin in combination with ascorbyl palmitate and vitamin D3 has been tested in a randomised, placebo-controlled, double-blind trial of 34 men and women (age 21–71 years) with diabetic neuropathy. The QR-333 preparation or placebo was applied three times daily for 4 weeks to each foot experiencing symptoms. QR-333 was well tolerated and reduced the severity of numbness, jolting pain and irritation from baseline values and improved quality of life (QOL) scores (Valensi et al 2005).

The diabetic status of rats fed high-dose quercetin (1 g/kg) was found to be ameliorated by approximately 25%; however, the amounts used were considerably higher than those commonly used in humans (Shetty et al 2004). Intraperitoneal injection of quercetin has also demonstrated an ability to improve glucose tolerance and cholesterol and triglyceride levels in diabetic, but not normoglycaemic, rats and increase the number of pancreatic islets in both groups (Vessal et al 2003). However, these results cannot necessarily be applied to oral doses in humans, and further research is required to confirm any potential benefits.

Cataracts

In addition to the potential reduction in diabetic cataract formation afforded by the inhibition of aldose reductase (Ramana et al 2007, Chaudhry et al 1983), quercetin may also reduce oxidative stress associated with the initiation of maturity-onset cataracts.

Cataracts may result from oxidative damage to the lens, which causes a disruption of the redox system, membrane damage, proteolysis, protein aggregation and a loss of lens transparency. Quercetin has been shown to inhibit oxidative damage to the lens and maintain lens transparency in vitro (Cornish et al 2002, Sanderson et al 1999). In rats with galactosaemic cataracts, quercetin improves lens transparency by maintaining the characteristic osmotic ion (calcium, sodium and potassium) equilibrium and protein levels of the lens (Ramana et al 2007). Further trials are warranted to confirm the effects of oral doses in humans.

Preventing cardiovascular disease

The cardioprotective properties of quercetin, demonstrated in animal and in-vitro studies, provide a theoretical basis for the use of quercetin in the prevention of cardiovascular disease; however, current human data are less encouraging.

A double-blind placebo-controlled study investigating the effects of a quercetin-containing supplement on plasma quercetin status, risk factors for heart disease and serum/platelet fatty acid levels was conducted on 27 healthy men and women with cholesterol levels of 4.0–7.2 mmol/L (Conquer et al 1998). The subjects consumed a quercetin-containing supplement (1 g quercetin/day) or rice flour placebo for 28 days. Quercetin intakes were approximately 50-fold greater than dietary intakes previously associated with lower coronary heart

disease mortality in epidemiological studies. Plasma quercetin concentrations were approximately 23-fold greater in subjects consuming the quercetin capsules than in the placebo group. Quercetin supplementation did not alter serum total, LDL or high density lipoprotein (HDL) cholesterol or triglyceride levels or other cardiovascular disease or thrombogenic risk factors such as platelet thromboxane B2 production, blood pressure or resting heart rate. This is in contrast to a previous trial (Hubbard et al 2004), which demonstrated inhibition of platelet aggregation and signalling and thrombus formation at a dose of 150 or 300 mg quercetin-4′-O-beta-D-glucoside. There was also no effect on the levels of omega-3 or omega-6 polyunsaturated fatty acids in serum or platelet phospholipids (Conquer et al 1998). Further investigation with larger and long-term trials is required to determine the effects and safety of quercetin in the prevention of cardiovascular disease in humans.

Metabolic syndrome

In obese rats, quercetin treatment (2 or 10 mg/kg of body weight for 10 weeks) resulted in a reduction in elevated systolic blood pressure, triglycerides, total cholesterol, free fatty acids and insulin. The higher dose also produced anti-inflammatory effects (Rivera et al 2008).

Chronic prostatitis

Thirty men with category IIIa or IIIb chronic pelvic pain syndrome received either placebo or quercetin 500 mg twice daily for 1 month. Sixty-seven per cent of the treated subjects had at least a 25% improvement in symptoms compared to 20% of the placebo group. In a follow-up, unblinded, open-label study, 17 additional men received the same dose of quercetin (combined with bromelain and papain to enhance absorption) for 1 month. The combination increased the response rate from 67 to 82% (Shoskes et al 1999). The anti-inflammatory, antioxidant and immunomodulating activities of quercetin may help to explain these results.

Cancer

Early concerns that quercetin may be carcinogenic have not been supported by recent research. Quercetin is primarily found in fruit and vegetables, which have been shown to decrease the risk of certain human cancers when consumed regularly (Morrow et al 2001), thereby casting doubt on this proposition. In fact, the anticarcinogenic effects of quercetin seen in laboratory animals suggest a possible preventative role (Erlund 2004), and in-vitro and epidemiological studies have suggested potential benefits in the prevention of colon (Kim et al 2005, Park et al 2005), lung (Schwarz et al 2005), prostate (Yuan et al 2004) and breast cancer (Otake et al 2000).

Human studies using extremely low-dose supplementation of quercetin (30 mg/day) have so far provided more questions than answers about the exact mechanism(s) by which quercetin may exert its effects but much remains unknown (Morrow et al 2001).

OTHER USES

Although the potential benefits of quercetin in allergic conditions have yet to be elucidated by human trials, quercetin is often used to treat conditions such as hayfever and other respiratory allergies and histamine-related conditions. In practice, quercetin is also commonly used to stabilise the integrity of blood vessel walls and address conditions resulting from capillary fragility and used in conjunction with vitamin C for the treatment of viral infections.

DOSAGE RANGE

General dose range

- 200–1500 mg daily taken in divided doses (PDR-Health 2005, Spoerke & Rouse 2004)

Specific doses

- Chronic prostatitis: 500 mg (combined with bromelain and papain to enhance absorption) twice daily (Shoskes et al 1999)
- Acute allergies: 2 g every 2 h for 2 days (often used with vitamin C)
- Chronic allergies: 2 g daily
- Asthma: as an adjunct to standard treatment 2 g daily

ADVERSE REACTIONS

Quercetin is generally well tolerated and appears to be associated with little toxicity when administered orally or intravenously (Lamson & Brignall 2000). Adverse effects may include nausea, dyspnoea, headache and mild tingling of the extremities (PDRHealth 2005, Spoerke & Rouse 2004).

SIGNIFICANT INTERACTIONS

Possible modulation of P-glycoprotein (Choi & Li 2005, Hsiu et al 2002, Limtrakul et al 2005) and inhibition of CYP1A1 (Schwarz et al 2005), CYP1A2 (Chang et al 2005) and CYP 3A4 (Choi & Li 2005) activity should be considered when prescribing.

Note: Phase II metabolites of quercetin appear to inhibit human multidrug resistance-associated protein 1 (MRP1) and 2 (MRP2), which may prove beneficial in MRP-mediated multidrug resistance (van Zanden et al 2007). For instance, the combined effect of quercetin with hyperthermia in human myelogenous leukaemia cells may assist in the reversal of multidrug resistance (Shen et al 2008).

Adriamycin

Quercetin has demonstrated a protective effect against adriamycin-induced cardiotoxicity in mice. The effect is likely to be related to enhanced myocardial SOD activity, decreased iNOS activity and inhibition of myocardial apoptosis (Pei et al 2007).

Cisplatin

Quercetin pretreatment may sensitise human cervix carcinoma cells to cisplatin-induced apoptosis (Jakubowicz-Gil et al 2005). Beneficial interaction is theoretically possible under professional supervision, but clinical significance is unknown.

Cyclosporin
Animal studies demonstrate that co-administration of quercetin significantly decreases the oral bioavailability of cyclosporin (Hsiu et al 2002) — avoid concurrent use.

Digoxin
An increase in drug bioavailability is theoretically possible and has been observed in an in-vivo study. Although human studies at lower doses are not available, the narrow therapeutic range of digoxin and the serious nature of the interaction should not be underestimated. Avoid concurrent use.

Diltiazem
Pretreatment of rabbits with quercetin resulted in an increased bioavailability of the calcium channel blocker, diltiazem, which may be the result of inhibition of P-glycoprotein and CYP 3A4 (Choi & Li 2005). Caution — use under professional supervision; doses may need to be adjusted accordingly.

Doxorubicin
Quercetin appears to significantly inhibit the formation of cardiotoxic doxorubicinol without affecting the transport of [14C]doxorubicin in human resistant breast cancer cells. It may therefore be useful in reducing doxorubicin-mediated toxicity (Vaclavikova et al 2008) under professional supervision.

Haloperidol
Tardive dyskinesia (rhythmical involuntary movements of the tongue, face, mouth or jaw, e.g. protrusion of tongue, puffing of cheeks, puckering of mouth and chewing movements) may result from long-term therapy with the antipsychotic medication haloperidol and may be irreversible in some individuals with no known effective treatment. Oxidative stress and the products of lipid peroxidation have been implicated in the pathophysiology of tardive dyskinesia, and co-administration of quercetin (25–100 mg/kg) has been shown to dose dependently reduce haloperidol-induced vacuous chewing movements and tongue protrusions in animal models (Naidu et al 2003). Beneficial interaction is theoretically possible under professional supervision.

Paclitaxel
Pretreatment with quercetin may increase the bioavailability of paclitaxel according to animal studies (Choi et al 2004). Caution — use under professional supervision; doses may need to be adjusted accordingly.

Paracetamol
According to animal data, pretreatment with quercetin may reduce the risk of mortality from paracetamol overdose (Janbaz et al 2004). However, effects in humans have not been studied — beneficial interaction theoretically possible.

Pioglitazone
Quercetin may increase the bioavailability of pioglitazone (Actos) (Umathe et al 2008). Due to the potential for toxicity, careful monitoring of hepatic and cardiac function is required — Caution.

Quinolone antibiotics
In vitro, quercetin binds to the DNA gyrase site in bacteria and therefore may theoretically compete with quinolone antibiotics that also bind to this site (PDRHealth 2005) — caution.

Saquinavir
Despite the inhibition of P-glycoprotein by quercetin, co-administration does not appear to alter plasma saquinavir concentrations. However, as there appears to be a substantial inter- and intra-subject variability in saquinavir intracellular concentrations, caution should be exerted until more is known (DiCenzo et al 2006).

Stibanate
Concurrent use of quercetin with the antileishmanial drug stibanate appears to improve the efficacy of the drug and reduce anaemia and parasitaemia associated with the condition (Sen et al 2005) — beneficial interaction theoretically possible.

CONTRAINDICATIONS AND PRECAUTIONS
Hypersensitivity to quercetin.

According to experimental studies, quercetin may possess some antithyroid properties, inhibiting thyroid cell growth in association with inhibition of insulin-modulated phosphatidylinositol 3-kinase-Akt kinase activity. While these findings are preliminary, quercetin should be used with caution in thyroid disease and therapy until more is understood about these effects in humans (Giuliani et al 2008).

PREGNANCY USE
Safety in pregnancy has not been established.

PRACTICE POINTS/PATIENT COUNSELLING
- Quercetin is a flavonol belonging to a group of polyphenolic substances known as flavonoids or bioflavonoids and is found in many fruits, vegetables and some herbal medicines.
- According to experimental studies, it has antioxidant, anti-inflammatory, antiviral, mast cell stabilisation, neuroprotective, gastroprotective, hepatoprotective and possibly cardioprotective actions.
- In practice, it is used for respiratory allergies such as hayfever, as an adjunct in asthma management, preventing diabetic complications such as cataracts and symptom relief in prostatitis; however, large controlled studies are not available to determine its effectiveness.
- Numerous drug interactions are theoretically possible, mainly due to P-glycoprotein and CYP inhibition.
- Quercetin is generally well tolerated. Adverse effects may include nausea, dyspnoea, headache and mild tingling of the extremities.

PATIENTS' FAQS

What will this supplement do for me?

Quercetin has several pharmacological effects and may provide some symptom relief in allergic conditions and prostatitis and may be beneficial in diabetes and cardiovascular disease; however, further research is required to clarify its effectiveness.

When will it start to work?

This will depend on the indication it is being used to treat.

Are there any safety issues?

Although it is generally well tolerated, numerous drug interactions are possible, so seek professional advice if taking other medication.

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Raspberry leaf

HISTORICAL NOTE Although the fruits of the raspberry are used as a luxury food source and in dietary drinks, midwives have used raspberry leaves since ancient times to prepare the uterus for childbirth. Raspberry has also been used as an antidiarrhoeal agent and an astringent to treat inflammations of the mucous membranes of the mouth and throat.

COMMON NAME
Red raspberry

OTHER NAMES
Framboise, *Rubi idaei folium*, rubus

BOTANICAL NAME/FAMILY
Rubus idaeus (synonym: *Rubus strigosus*) (family Rosaceae [roses])

PLANT PART USED
Leaf

CHEMICAL COMPONENTS
Raspberry leaves have a tannin content of between 13% and 15%, as well as phenolic compounds like the flavonoids rutin and quercetin, volatile oils, organic acids and vitamin C.

MAIN ACTIONS
Raspberry leaf contains a number of active constituents and their therapeutic actions have been reviewed (Patel et al 2004). Currently, evidence of activity comes from in vitro and in vivo studies.

Uterine effects
Raspberry leaf has demonstrated a variable effect on uterine muscle tone as it contains a smooth muscle stimulant, an anticholinesterase and an antispasmodic. The results of animal studies indicate that raspberry can either reduce or initiate uterine contractions (Bamford et al 1970). It appears to inhibit uterine contractions in samples from pregnant test animals, but has no effect in non-pregnant ones. Samples from human pregnant uteri respond with contraction effects; however, no effect was seen on non-pregnant uteri samples. Overall, it appeared that raspberry leaf extract promoted more regular contractions that generally became less frequent (Newell et al 1996). A more recent preliminary study produced similar results with fractions of raspberry leaf extract, both stimulating and relaxing uterine muscle in pregnant rats (Briggs & Briggs 1997). There is evidence of at least two components of raspberry leaf extract that exhibit relaxant activity in an in vitro guinea pig ileum preparation (Rojas-Vera et al 2002). Results imply a regulatory action on contractions.

Antidiarrhoeal
In addition to the high tannin content of the leaves which may exert an antidiarrhoeal action, raspberry cordial and juice, made from the fruits, were found to significantly reduce the growth of several species of gut bacteria, including *Salmonella*, *Shigella* and *Escherichia coli*. However, no antimicrobial activity was detected in the leaf extract or tea (Ryan et al 2001).

Anti-inflammatory
Raspberry leaf exhibits anti-inflammatory activity because of its high tannin content, which has been found to inhibit COX (Duke 2003). When applied topically to mucous membranes, tannins have a local anti-inflammatory effect, produce capillary vasoconstriction and decrease vascular permeability (Halvorsen et al 2001).

Astringent
The high tannin content of the leaf is responsible for the astringent activity.

OTHER ACTIONS
The phenolic content of raspberry leaves may provide antioxidant protection against oxidative stress that can induce neuronal damage. Raspberry ketone, which is an aromatic compound with similar structure to capsaicin and synephrine, has been shown in vivo to prevent and improve obesity and fatty liver though increasing noradrenaline-induced lipolysis in white adipocytes (Morimoto et al 2005).

CLINICAL USE
The therapeutic effects of raspberry have not been significantly investigated under clinical trial conditions, so most evidence is derived from traditional, in vitro and animal studies.

Uterine tonic
Raspberry leaf is commonly used as a 'partus preparator' to prepare the uterus for delivery and to facilitate labour, as well as for treating morning sickness, dysmenorrhoea, leucorrhoea and menorrhagia (McFarlin et al 1999). A study of 588 pregnant women of 36–38 weeks' gestation who were attending a public tertiary maternity hospital in Melbourne, Australia were surveyed to measure the prevalence of herbal medicine use in pregnancy. Thirty-six percent of women took at least one herbal supplement during the current pregnancy, their most common supplement being raspberry leaf (14%).

In vitro studies using pregnant rat and human uteri preparations suggest that raspberry may increase the regularity and decrease the frequency of uterine contractions (Bamford et al 1970). In a double-blind trial of 192 low-risk nulliparous women, raspberry leaf (2 × 1.2 g/day), consumed from 32 weeks' gestation until labour, was associated with a lower rate of interventions with no adverse effects for mother or baby (Simpson et al 2001). Raspberry leaf did not shorten the first stage of labour; however, it did significantly reduce the second stage. A retrospective, observational study of 108 mothers also found that treatment with raspberry leaf was associated with a lower rate of medical intervention (Parsons et al 1999). This study further suggested that treatment may shorten labour, and reduce the incidence of pre- and post-term labour. Some pregnant women commenced use of raspberry leaf from 8 weeks' gestation; however, most chose to start it between 30 and 34 weeks' gestation.

Topical inflammatory conditions
The high tannin content of raspberry supports its traditional use as a topical treatment for inflammation of the mouth, throat, eye and skin, as well as to treat cuts and wounds.

Diarrhoea
Once again, the high tannin content of raspberry supports its traditional use as an antidiarrhoeal agent.

Dyspeptic complaints
Traditionally understood to act as a choleretic, raspberry leaf is used to improve digestion and detoxifying processes, but controlled studies are not available to determine its effectiveness.

OTHER USES
Raspberry leaf is commonly recommended for nausea and vomiting in pregnancy, but this advice is based more on anecdotal evidence than rigorous scientific evidence, highlighting a need for more research in this area.

Cold infusions of raspberry leaf have been used to treat diarrhoea, loose bowels and stomach complaints in children. Raspberry leaf has traditionally been incorporated into mouthwashes to treat inflammation of the mouth and throat, used as a diaphoretic for fever, as a choleretic to improve digestion and detoxification, and as a food and flavouring agent.

In a small, uncontrolled, prospective pilot study of eight women, raspberry leaf in combination with

11 other botanical extracts was found to relieve menopausal symptoms (Smolinski et al 2005).

DOSAGE RANGE

Internal use

- Infusion of dried leaf: 4–8 g taken up to three times daily.
- Liquid extract: (1:1): 4–8 mL three times daily.

External use

- Topically, the tea can be used as a mouth or eye wash, or to clean wounds.

TOXICITY

There is no evidence that raspberry leaf tea is toxic.

ADVERSE REACTIONS

Owing to the tannin content of the herb, it may cause gastrointestinal discomfort.

SIGNIFICANT INTERACTIONS

Iron, calcium, magnesium

Due to its high tannin content, raspberry leaf may decrease absorption of iron, calcium and magnesium, as well as some drugs. As such, it is advised to separate the administration of these substances by at least 2 h.

CONTRAINDICATIONS AND PRECAUTIONS

The high tannin concentration within the herb means it should be avoided in constipation and used cautiously in active peptic ulcer and gastrointestinal conditions associated with inflammation.

PREGNANCY USE

There is no evidence of harmful effects on the fetus, despite consumption by a large number of women. Clinical studies suggest that it is safe to use after the first trimester, although it is prudent to ensure close professional supervision.

PATIENTS' FAQs

What will this herb do for me?

Raspberry leaf preparations have been used since ancient times to prepare the uterus for birth in an attempt to facilitate a complication-free labour. It is also used to treat diarrhoea and dyspeptic complaints, and incorporated into a mouthwash to reduce inflammation of the mouth and throat.

When will it start to work?

Currently, there is insufficient research to answer this question. However, it is used in increasing doses during the last few weeks of pregnancy. Symptomatic relief of diarrhoea and inflammation of the oral cavity is likely to occur within the first few doses.

Are there any safety issues?

Considering that raspberry leaf has uterine activity, it is recommended that pregnant women wanting to use it do so under the careful supervision of an experienced healthcare professional.

PRACTICE POINTS/PATIENT COUNSELLING

- Raspberry leaves have been traditionally used to prepare the uterus for childbirth, with some modern research suggesting that they may be useful.
- When used in this way, raspberry leaf is often combined with other herbs and used during the last 6–8 weeks of pregnancy under close supervision.
- Raspberry leaves are high in tannins, which may make them useful as a mouthwash and to treat diarrhoea, although this has not been confirmed in clinical trials.
- As tannins may reduce the absorption of other substances, it is recommended to take raspberry leaf preparations separately from other medications. Raspberry leaf preparations can be considered safe and non-toxic.

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Red clover

HISTORICAL NOTE Red clover has been used for a long time as an animal fodder as well as a human medicine. Traditionally, it is considered as an alterative remedy with blood cleansing properties useful in the treatment of skin diseases such as psoriasis, eczema and rashes. A strong infusion was used to ease whooping cough and other spasmodic coughs due to measles, bronchitis and laryngitis. It was recommended for 'ulcers of every kind, and deep, ragged-edged, and otherwise badly-conditioned burns. It possesses a peculiar soothing property, proves an efficient detergent, and promotes a healthful granulation'. Combined with other herbs, red clover was recommended for syphilis, scrofula, chronic rheumatism, glandular and various skin affections (Felter & Lloyd 1983). Interestingly, red clover was not traditionally used for the treatment of menopausal symptoms.

OTHER NAMES

Cow clover, meadow clover, purple clover, trefoil

BOTANICAL NAME/FAMILY

Trifolium pratense L. (family Fabaceae)

PLANT PARTS USED

Flower head or leaf

CHEMICAL COMPONENTS

Flower head

Flavonoids, including formononetin; flavonols, including isorhamnetin and quercetin glucosides; phenolic acids, including salicylic and p-coumaric acids; volatile oils and other constituents, including sitosterol, starch, fatty acids (British Herbal Medicine Association Scientific Committee 1983).

Leaf

Isoflavones, including biochanin A, daidzein, formononetin and genistein; caffeic acid derivatives; and coumestrol (trace) (Clifton-Bligh et al 2001, He et al 1996).

In the plant, the isoflavones are attached to a sugar molecule, usually glucose. The chemical term for any compound attached to a sugar is 'glycoside'. The free isoflavone form is known as an 'aglycone'. The active aglycone is liberated in the gut. Isoflavones are readily absorbed from the gut; they circulate freely in the blood and are excreted in the urine; 50% of ingested isoflavones are eliminated within 12 h (Joannou et al 1995).

The aglycone forms of the four main oestrogenic isoflavones are genistein, daidzein, biochanin and formononetin.

MAIN ACTIONS

Oestrogenic activity

The pharmacological investigation of red clover has mainly centred around the activity of the isoflavone constituents, especially their oestrogenic activity (Miksicek 1994). Red clover products contain primarily formononetin and biochanin A. The isoflavones have varying levels of subtle oestrogenic activity, biochanin A having the strongest effect. Red clover isoflavones have been shown to have an affinity for oestrogen alpha- and beta-receptors and may act as both agonists and antagonists, depending on the level of endogenous oestrogens (Nelson et al 2006, Zava et al 1998). The isoflavones in red clover (and soy extracts) act as selective oestrogen receptor modulators (SERMs) as well as selective oestrogen enzyme modulators (SEEMs). The higher affinity of isoflavones to oestrogen beta-receptors compared to oestrogen alpha-receptors has been used to explain why red clover extracts treat menopausal disorders, reduce risk of breast cancer and have protective effects on osteoporosis and the cardiovascular system (Beck

Clinical note — Phyto-oestrogens and isoflavones

Phyto-oestrogens are plant-based compounds that are structurally similar to oestradiol. The term phyto-oestrogen encompasses isoflavone compounds, such as genistein and daidzein, found predominantly in soy and red clover, and the lignans, such as matairesinol and secoisolariciresinol, found in many fruits, cereals and in linseed. Phyto-oestrogens have been investigated for their potential to reduce the risk of hormone-dependent diseases such as breast and prostate cancers and osteoporosis. The metabolism of isoflavones and lignans is complex and involves gut microbial processes. Isoflavones are present predominantly as glucosides; however, their bioavailability requires initial hydrolysis of the sugar moiety by intestinal beta-glucosidases. After absorption, phyto-oestrogens are reconjugated predominantly to glucuronic acid and to a lesser degree to sulfuric acid. There is further metabolism of isoflavones (to equol and O-desmethyl-angolensin) and lignans (to enterodiol and enterolactone) by gut bacteria. In humans, even those on controlled diets, there is large inter-individual variation in the metabolism of isoflavones and lignans, particularly in the production of the gut bacterial metabolite equol (from daidzein). Dietary factors and gut microflora directly influence the absorption and metabolism of phyto-oestrogens and is likely to influence the clinical benefits of supplementation with phyto-oestrogens (Rowland et al 2003).

et al 2005). Animal studies show that red clover extract, standardised to contain 15% isoflavones, produced a dose-dependent increase in uterine weight and differentiated vaginal cells, but did not stimulate cell proliferation in mammary glands in an ovariectomised rat model. The extract did not produce any anti-oestrogenic or additive oestrogenic effects when combined with 17-beta-oestradiol (Burdette et al 2002). Supplementing isoflavones, either daidzein (at 100 mg/kg) or red clover extract (at 6.68 mg/kg), in menopausal rabbits also showed significant improvements in bone density, tissue integrity and vaginal blood flow with minimal effect on uterine weight (Adaikan et al 2008).

Antioxidant activity

The isoflavones in red clover display antioxidant activity at concentrations well within the range found in the plasma of subjects consuming soy products even though they undergo extensive metabolism in the intestine and the liver (Rufer & Kulling 2006).

Opioid activity

A new understanding of a potential mechanism of action for red clover has been identified which involves interaction with opiate receptors. Red clover extract has high binding affinity for the mu-opiate receptor and also affinity at the delta-opiate receptor. Given the essential role of the opioid system in regulating temperature, mood and hormonal levels this newly identified activity provides further rationale for its investigation as a treatment for relieving menopausal symptoms (Nissan et al 2007).

Reducing cancer risk

Phyto-oestrogens and isoflavones may reduce the risk of cancer, including breast cancer; however, the evidence is still not definitive (Adlercreutz et al 1995, Clarke et al 1996, Ingram et al 1997, Pagliaaci et al 1994). Biochanin A isolated from red clover has been shown to be antimutagenic, as well as protective against chemically induced DNA damage in vitro (Chan et al 2003). Genistein has been shown to inhibit cell proliferation and in vitro angiogenesis (Fotsis et al 1995).

An animal study has found that red clover isoflavones significantly increase oestrogen beta-receptor and E-cadherin expression, but decrease transforming growth factor beta-1. These proteins are markers of oestrogen-induced proliferation, preservation of cell phenotype and reduction of the potential for neoplastic and metastatic transformation. These results suggest that red clover isoflavones may be useful in the treatment of prostatic hyperplasia and reduce the risk of neoplastic transformation (Slater et al 2002). A study has reported that red clover-derived isoflavones significantly reduced non-malignant prostatic growth in mice by acting as antiandrogenic agents rather than weak oestrogenic substances (Jarred et al 2003). The metabolites of the red clover isoflavone, biochanin, are thought to contribute to its chemopreventive effects.

Biochanin A, daidzein and genistein have demonstrated antiproliferative activity in vitro (Hempstock et al 1998). In a recent in vitro study, red clover isoflavones were tested for their potential in transactivating aryl hydrocarbon receptor (AhR), which is known to affect the cell cycle and drive cells to apoptosis. Selective AhR modulators (SAhRMs) have previously been implicated in cancer therapy and prevention, particularly for hormone-dependent cancers. It was found that the isoflavones biochanin A and formononetin were potent AhR agonists in vitro, 10 times more potent compared to the indole compounds (Medjakovic & Jungbauer 2008). Red clover isoflavones (50 mg total isoflavones), however, were found not to be antiproliferative in a double-blind, randomised study of 30 perimenopausal women (Hale et al 2001).

CLINICAL USE

Considerable research has been carried out on the constituents of red clover; however, very few investigations have concentrated specifically on the flower heads and the traditional uses.

Relief of menopausal symptoms

Numerous clinical studies have been conducted using red clover extracts or isoflavones, which are found in red clover in varying concentrations. Many isoflavone studies do not report whether these constituents were derived from red clover or other sources making interpretation of the data difficult.

Red clover extract studies

The general consensus from systematic reviews and meta-analyses is that there is a lack of evidence to support the use of monopreparations containing *Trifolium pratense* isoflavones as a means of significantly reducing hot flush frequency, severity or other menopausal symptoms (Booth et al 2006, Cheema et al 2007, Coon et al 2007, Lethaby et al 2007, Low Dog 2005, Nelson et al 2006).

The most recent meta-analysis evaluated data from five randomised clinical trials of monopreparations containing *Trifolium pratense* isoflavones (40–82 mg daily) and concluded that active treatment resulted in a marginally significant effect reducing frequency of hot flushes in menopausal women, although the size of this effect may not be considered clinically relevant (Coon et al 2007). In 2007, Lethaby et al also reported in their systematic review that of the five trials with data suitable for pooling that assessed daily frequency of hot flushes, there was no significant difference overall in the frequency of hot flushes between Promensil (a red clover extract) and placebo. Furthermore, a systematic review by Low Dog et al (2005) stated the largest study showed minimal to no effect in reducing menopausal symptoms.

Isoflavone studies

Several reviews have evaluated the clinical evidence relating to isoflavone treatment in the relief of menopausal hot flushes finding conflicting and ambiguous results. Some of this confusion may arise from the fact that a variety of isoflavone sources

have been tested, often without discriminating between the identities of individual isoflavones or the different concentrations contained in the tested intervention product. As such, volunteers may be receiving greatly different doses or ranges of specific isoflavones from the different test products, but researchers have not taken this into account when evaluating and comparing results.

A review by Williamson and Hughes highlights this issue and the importance of clearly defining the chemical composition of isoflavone treatments in research reports. The authors evaluated results from 11 studies that tested similar total isoflavone doses (Williamson-Hughes et al 2006). Five of the eleven studies (n = 177) reported a statistically significant decrease in hot flush symptoms. Later evaluation revealed that the test products used in these studies provided more than 15 mg genistein (calculated as aglycone equivalents) per treatment. Of the remaining six studies (n = 201), five failed to find a significant decrease in hot flush symptoms. Participants in these studies received less than 15 mg genistein per treatment. Thus, the reduction in hot flushes was related to genistein content and not total isoflavone content of the treatments.

Interestingly, a 12-month, prospective, randomised, double-blind, placebo-controlled study demonstrated that the phytoestrogen genistein (54 mg/day) from red clover reduced the number and severity of hot flushes in postmenopausal women with no adverse effect on the endometrium (D'Anna et al 2007).

In combination

A nutritional supplement containing isoflavones from kudzu and red clover, along with other targeted nutrients, produced a 46% decrease in hot flush frequency, and quality of life, as assessed by the standardised Greene Questionnaire, showed similar improvement in a small pilot study of 25 menopausal women suffering from severe hot flushes and night sweats (Lukaczer et al 2005). A modest improvement in the ratio of total cholesterol to high-density lipoprotein (HDL) cholesterol was also observed and a statistical improvement in a proposed marker of breast cancer risk (the ratio of 2-hydroxyestrone to 16 alpha-hydroxyestrone) was also demonstrated. Whilst promising, the role of red clover in achieving these results remains unknown.

Other potential benefits in menopause

A randomised controlled trial using a standardised extract of red clover found that red clover exerts a moderate effect on testosterone levels in postmenopausal women, while oestradiol levels remained unchanged (Imhof et al 2006). The significance of this finding for clinical practice remains unknown.

Cardiovascular effects

Lipid lowering

A 2006 systematic review of randomised controlled trials, which included peri- or postmenopausal women, concluded that red clover extracts reduce levels of triglycerides and increase high-density lipoprotein cholesterol (Geller & Studee 2006). Given the lack of serious safety concerns in the short term, it would appear that including red clover in the diet of postmenopausal women might be beneficial. There is little convincing evidence that red clover extract significantly reduces total cholesterol or LDL cholesterol levels.

A randomised, placebo-controlled, crossover study of 60 postmenopausal women found that red clover isoflavones (80 mg/day) significantly decreased total cholesterol, LDL cholesterol and lipoprotein A levels in women with BMI > 25 kg/m^2 but not women with lower BMI (Chedraui et al 2008).

Blood pressure

Clinical studies have not consistently shown red clover isoflavones to significantly reduce blood pressure (Atkinson et al 2004b, Teede et al 2003); however, there is evidence that red clover isoflavones reduce arterial stiffness and total vascular resistance (Fugh-Berman & Kronenberg 2001, Nestel et al 1999, Teede et al 2003). A reduction in blood pressure and improved endothelial function was reported for red clover isoflavones (approximately 50 mg/day) in a small randomised, double-blind, crossover trial (n = 16) involving postmenopausal women with type 2 diabetes (Howes et al 2003).

Given the lack of serious safety concerns, red clover supplementation might be beneficial for postmenopausal women to reduce cardiovascular risk.

Reducing cancer risk

Much of the research in this area has focussed on isoflavones generally derived from soy products rather than red clover sources. As such, it is uncertain whether the results from these studies can be extrapolated to red clover extracts. For more information about the association between soy isoflavones and cancer risk, refer to the soy monograph.

Prostate cancer

A non-randomised, non-blinded trial of 38 men with clinically significant prostate cancer found that 160 mg/day red clover-derived dietary isoflavones, containing a mixture of genistein, daidzein, formononetin and biochanin A, significantly increased apoptosis compared with matched controls (P = 0.0018). There were no significant differences between pre- and post-treatment serum levels of prostate-specific antigen, testosterone or biochemical factors or Gleason score in the treated patients ($P > 0.05$). The study was performed in men undergoing radical prostatectomy; however, it indicates that the isoflavones may halt the progression of prostate cancer by inducing apoptosis in low-to-moderate grade tumours (Gleason grade 1–3) (Jarred et al 2002).

Breast cancer

A 2006 systematic review of complementary and alternative therapeutic approaches, including the use of red clover, in patients with early breast cancer drew the conclusion that available data on complementary and alternative medicine modalities in the treatment of early-stage breast cancer does not support their application (Gerber et al 2006).

Benign prostatic hypertrophy

Isoflavone-containing food and supplements are widely used in patients with benign prostatic hypertrophy (BPH). An in vivo study using mice showed that red clover-derived isoflavones have a significant effect on prostatic growth, and are capable of reducing the tendency to enlarged non-malignant prostate, by acting as antiandrogenic agents rather than weak oestrogenic substances (Jarred et al 2003). A case series (n = 29) presented at the Endocrine Society's 82nd Annual Meeting in 2000 suggested that 3 months of treatment with one or two tablets of Trinovin (standardised to 40 mg red clover isoflavones per tablet) significantly decreased nocturia frequency, the International Prostate Symptom Score, increased urinary flow rates and quality of life (QOL) score. The prostate specific antigen (PSA) values and prostate size did not alter from baseline (Ulbricht & Basch 2005). A small clinical trial involving 20 men aged over 65 years with elevated prostate-specific antigen (PSA) levels and negative prostate biopsy findings showed that oral administration of a red clover isoflavone extract (60 mg/day) significantly decreased total PSA levels by >30%. During the 1-year treatment period, active treatment was well tolerated and caused no side effects and significantly increased liver transaminases (an indication of improved liver function) were observed (Engelhardt & Riedl 2008).

Osteoporosis prevention

Pharmaceutical hormone replacement therapy (HRT) is sometimes used for preventing loss of bone following menopause; however, a growing number of users are concerned about the increased risk of breast cancer associated with long-term HRT. As such, phyto-oestrogens have been used as an alternative to prevent osteoporosis. Most research has focused on soy isoflavones, although there is some evidence that red clover-derived isoflavones may also be of benefit.

Animal studies have demonstrated that red clover isoflavones are effective in reducing bone loss probably by reducing of the bone turnover via inhibition of bone resorption (Occhiuto et al 2007). However, human studies show variable results. In a trial by Atkinson et al, loss of lumbar spine bone mineral content and bone mineral density was significantly reduced in women taking red clover-derived isoflavones (43.5 mg/day) compared to placebo in a double-blind, placebo-controlled, randomised trial in 205 women over 12 months (Atkinson et al 2004a). Bone formation markers were also significantly increased; however, no improvement in hip-bone mineral content or bone mineral density was noted. A double-blind study of 46 postmenopausal women investigated the effects of a red clover isoflavone preparation (Rimostil) containing genistein, daidzein, formononetin and biochanin A after a single-blind placebo phase and followed by a single-blind washout phase. Patients were randomly assigned to receive 28.5 mg, 57 mg or 85.5 mg phyto-oestrogens daily for a 6-month period. After the test period, the bone mineral density of the proximal radius and ulna rose significantly, by 4.1% with a dose of 57 mg/day and by 3.0% with a dose of 85.5 mg/day isoflavones. The response with 28.5 mg/day isoflavones was not significant (Clifton-Bligh et al 2001).

No significant difference in bone turnover markers was apparent after 12 weeks of treatment with Promensil and Rimostil in a double-blind, placebo-controlled, randomised clinical trial in 252 menopausal women aged between 45 and 60 years (Schult et al 2004).

OTHER USES

Several human and animal studies have attributed hypolipidaemic, hypoglycaemic or antiatherosclerotic effects to red clover extract or isoflavones. Red clover isoflavones extract exert a neuroprotective effect in human cortical neurons in vitro, which may be due to antioxidant and oestrogenic actions (Occhiuto et al 2008, 2009).

An animal study to investigate the effects of red clover isoflavones on skin ageing, the histology of the skin, skin thickness and the amount of total collagen, with a red clover extract standardised to contain 11% isoflavones concluded that red clover isoflavones are effective in reducing skin ageing induced by oestrogen deprivation (Circosta et al 2006).

TRADITIONAL USES

Red clover flower heads are traditionally used for indications not related to the potential hormonal activity of the herb. The alterative or blood cleansing action is used in skin eruptions and as part of treatment for cancer. A poultice of red clover flowers can be used to soothe local inflammations such as acne, burns or ulcers.

The British Herbal Pharmacopoeia lists red clover as a dermatological agent, mild antispasmodic and expectorant (British Herbal Medicine Association Scientific Committee 1983). The specific indications are for eczema and psoriasis. Red clover is said to combine well with yellow dock for treatment of chronic skin disease.

DOSAGE RANGE

- 4 g as infusion or extract.
- Liquid extract (1:1) in 25% alcohol: 1.5–3.0 mL/day.
- Concentrated isoflavone extract containing 40–80 mg total isoflavones are recommended, based on the daily intake of phytoestrogens in a traditional Japanese diet.

Note: The isoflavone content of the marketed red clover products is highly variable and this alone may significantly affect the absorption rates.

According to clinical reports

- Menopausal symptoms: 40–82 mg daily of red clover-derived isoflavones.
- Lipid lowering: 40–86 mg daily of red clover-derived isoflavones.
- Osteoporosis prevention: 44–86 mg daily of red clover-derived isoflavones.
- BPH symptom relief: 40–80 mg daily of red clover-derived isoflavones.

ADVERSE REACTIONS

The oestrogenic potency of the isoflavones has been well documented. Overgrazing cattle or sheep on red clover can be detrimental to their fertility. In 'clover disease', ewes are made permanently infertile by clover consumption. In animals with clover disease, the uterine response to oestrogen is reduced, as is the surge in LH. Clover disease has not been observed with normal therapeutic doses in humans. None of the trials has reported adverse effects. An isoflavone preparation from soy bean, and red clover extracts containing genistein, daidzein, biochanin A and formononetin, did not modify the endometrial architecture in 25 postmenopausal women taking the preparation for 1 year (Aguilar et al 2002).

SIGNIFICANT INTERACTIONS

Controlled studies are not available; therefore, interactions are based on evidence of activity and are largely theoretical and speculative.

Anticoagulant agents

Red clover contains coumarin, which could theoretically exert anticoagulant activity and therefore increase the clinical effects of warfarin. However, it is only the byproduct, dicoumarol (produced by microorganism in poorly dried sweet clover), that has established anticoagulant effects. However, interaction with anticoagulant medication is not likely for extracts from properly dried red clover. Observe patients taking red clover and anticoagulants concurrently.

Oestrogens

Theoretically, if taken in large quantities, phytoestrogens may compete with synthetic oestrogens for receptor binding, but the clinical significance of this remains unknown. A recent review concluded that up to 2 mg of red clover-derived isoflavones per kg should be considered a safe dose for most patient groups (Barnes 2003).

CONTRAINDICATIONS AND PRECAUTIONS

There are no known contraindications for the flower head extracts. Concentrated isoflavone extracts should only be used by people with oestrogen-sensitive cancers under professional supervision because of the possible proliferative effects. Additionally, people with conditions that may be aggravated by increased oestrogen levels, such as endometriosis or uterine fibroids, should use this herb under professional supervision only. Importantly, no randomised controlled trials have addressed the long-term safety of phytoestrogens in patients after a diagnosis of breast cancer (Boekhout et al 2006).

Red clover isoflavones are well tolerated in healthy women according to a 3-year study of 400 women. Supplements containing red clover isoflavones did not adversely affect breast density, skeletal strength or cardiovascular status. In postmenopausal women, endometrial status was not adversely affected. The adverse event profile was similar between red clover isoflavones, and placebo and endocrine status did not differ (Powles et al 2008).

PREGNANCY USE

Scientific evidence for the use of red clover during pregnancy has not been established. No teratogenicity data are available — use is not recommended.

PRACTICE POINTS/PATIENT COUNSELLING

- Red clover flower heads are traditionally considered a dermatological agent, mild antispasmodic and expectorant and specifically used for eczema and psoriasis. In practice, it is often combined with yellow dock for treatment of chronic skin disease.
- In recent years, red clover isoflavones have been studied and shown to have an affinity for oestrogen alpha- and beta-receptors and may act as both agonists and antagonists, depending on the level of endogenous oestrogens.
- Evidence that red clover-derived isoflavones reduce hot flush frequency in menopause is unconvincing.
- Preliminary evidence suggests a possible preventative role in osteoporosis; however, further research is required.
- Concentrated isoflavone extracts from red clover are used in cardiovascular disease as there is weak evidence that it may reduce arterial stiffness, increase HDL cholesterol and decrease triglycerides.
- Evidence from animal studies and case series suggests a potential role in BPH.
- There is weak evidence that red clover isoflavone extracts may reduce risk of hormone-sensitive cancers and that they may be beneficial in the treatment of prostate cancer.

PATIENTS' FAQS

What will this herb do for me?

Red clover is traditionally used for skin disorders. In recent years, concentrated red clover isoflavone extracts have been promoted for use in the treatment of menopausal symptoms, although clinical studies are inconsistent and generally unsupportive.

When will it start to work?

Red clover tea or extract for skin diseases requires long-term use. Improvement may occur within several weeks with the condition continuing to improve with long-term use. Improvement in menopausal symptoms from the use of concentrated isoflavone extracts may take 2–3 months, although results are inconsistent.

Are there any safety issues?

Short- or long-term use of red clover tea or flower head extract is not thought to be associated with any adverse reactions and its use is considered safe. Concentrated red clover isoflavone extracts may have subtle oestrogenic activity and little is known about drug interactions or long-term use. As a result, they should not be used by people with oestrogen-sensitive tumours or conditions that may be aggravated by increased oestrogen levels such as endometriosis, unless under professional supervision. People with breast cancer should only use red clover extracts under professional supervision.

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Red yeast rice

HISTORICAL NOTE Red yeast rice, also known as red Koji or 'Hongqu', is a dietary staple in many Asian countries, including China and Japan, and has been used as a food, medicine and seasoning for more than a thousand years. Li Shizhen, the great pharmacologist of the Ming Dynasty (1368–1644), reported that 'Hongqu' promotes 'digestion and blood circulation, and can strengthen the spleen and dry the stomach' (Ma et al 2000). Red yeast rice, which is produced by fermenting steamed, non-glutinous rice with *Monascus* species of food fungus, is widely used in making pickled tofu, for brewing rice wine and as a preservative for meat and fish, thereby giving many dishes such as Peking duck their characteristic red colour.

In recent years, several commercial versions of red yeast rice have been made available and red yeast rice has been included by the Chinese Ministry of Health into food additive standards to increase the colour and delicacy of meat, fish, and soybean products. In 1979, Prof Akira Endo, working in Japan on fungicides, found that *Monascus purpureus* on rice contained a compound that he called 'Monacolin K', which was identified as a new hypocholesterolaemic agent that specifically inhibits HMG-CoA reductase (Endo 1980). This discovery led to the development of a new class of anticholesterol drugs now called the 'statins'.

COMMON NAME

Red yeast rice (RYR)

OTHER NAMES

Chinese red yeast rice, Red Koji, Hongqu, Hon-Chi, Beni-koji. Zhi Tai is the dried, powdered form while Xue Zhi Kang is a standardised ethanolic extract.

BOTANICAL NAME/FAMILY

RYR is produced by fermenting cooked rice with various *Monascus* species, most commonly *Monascus pilous* and *Monascus purpureus*.

CHEMICAL COMPONENTS

RYR is a food and medicine with a range of potentially active and synergistic constituents. While it is assumed that the main active constituents are the monacolins, particularly monacolin K or lovastatin along with a range of other monacolins, there are a number of other potentially active constituents such as plant sterols, isoflavones and isoflavone glycosides, pigments, tannins and other phytochemicals that may act synergistically to produce clinical effects. This is evident by the finding that the cholesterol-lowering effect of RYR is greater than that of an equivalent dose of lovastatin (Li Z et al 2005b).

The monacolin content of traditionally produced RYR has been found to vary widely (Huang et al 2006, Li et al 2004). This may be due to variations in *Monascus* species, growing and storage conditions, as monacolin levels are influenced by exposure to light and heat (Li YG et al 2005). A study that examined the chemical constituents of nine different commercially available RYR supplements found that total monacolin content varied from 0% to 0.58% w/w and that only one of nine preparations had the full complement of 10 different monacolin compounds (Heber et al 2001).

As a fermented food, RYR may contain differing levels of the hazardous mycotoxin, citrinin, which has been found at measurable concentrations in seven of nine commercial preparations (Wong & Rabie 2008). Modern production methods aim to standardise the monacolin content and minimise the citrinin content (Soo et al 2007).

MAIN ACTIONS

Cholesterol lowering

RYR has significant lipid-lowering activity which is due to multiple mechanisms. One of the most studied is inhibition of HMG-CoA reductase.

Inhibition of HMG-CoA reductase, which is the rate-limiting enzyme in cholesterol biosynthesis, causes a decrease in cholesterol synthesis, which leads to up-regulation of LDL receptors, increasing the rate of removal of LDL from plasma. RYR contains natural statin components that inhibit HMG-CoA reductase and hence reduce cholesterol synthesis in human hepatic cells in a dose-dependent manner (Man et al 2002).

RYR has also been found to reduce serum total cholesterol and triglycerides in rabbits and quails with experimental hyperlipidaemia and suppress atherosclerosis induced by atherogenic diets (Li et al 1997). The authors of this study suggest that the lipid-lowering mechanism of red yeast rice is not completely understood and may be due to the

combination of its total constituents exerting multiple mechanisms including inhibiting in vivo biosynthesis of cholesterol, preventing the absorption of ingested cholesterol, or increasing cholesterol clearance from the circulation.

In animal studies, RYR significantly reduces serum lipids and the severity of atherosclerosis in rabbits fed for 200 days on a semi-purified diet containing 0.25% cholesterol. Treatment resulted in a significant reduction in atherosclerotic index (ratio of non-HDL cholesterol to HDL cholesterol). Interestingly, although similar reductions of total, LDL cholesterol and triglycerides were observed in a parallel group of rabbits fed 2.4 mg/kg/day of lovastatin, the lovastatin group did not have a significant reduction in atherosclerotic index (Wei et al 2003).

As well as reducing cholesterol, RYR may also have positive effects on endothelial function by reducing homocysteine-stimulated endothelial adhesiveness, as well as down-regulating intracellular reactive oxygen species (ROS) formation (Lin et al 2008). It has also been observed that RYR extract (Xuezhikang) significantly enhanced proliferation and adhesion capacity of endothelial progenitor cells derived from the peripheral blood of patients with stable coronary artery disease to the same extent as atorvastatin (Kong et al 2008).

Anti-inflammatory

Recent studies suggest that in addition to lowering cholesterol, the statin drugs may have potent vascular anti-inflammatory actions that produce reductions in vascular plaque adherence and migration to sites of inflammation in atherosclerosis. This has led to the suggestion that low-dose statins may be used for long-term treatment of cardiovascular disease in susceptible individuals (Liao 2004). Interestingly, trials have demonstrated anti-inflammatory properties for RYR. In a randomised controlled trial involving 36 patients with cardiovascular disease, 1200 mg/day of a RYR extract (Xuezhikang) was found to significantly reduce C-reactive protein (CRP) and other inflammatory markers and prolong exercise tolerance and time to 1-mm ST-segment depression, in addition to significantly reducing total cholesterol, LDL cholesterol and triglycerides (Li et al 2007). Similarly, the same extract was found to produce significant reductions in CRP within 24 hours (Li JJ et al 2005a), reduce CRP levels and improve preprandial and postprandial endothelial function after 6 weeks in patients with coronary heart disease (Liu et al 2003, Zhao et al 2004). These findings have led to the suggestion that the inclusion of RYR in Asian diets may contribute to the median CRP level of Asians being only one-tenth that of Westerners (Kao et al 2006).

Anticancer

Epidemiological studies demonstrate that individuals taking statins have a reduced risk of colon cancer. RYR and lovastatin have been shown to inhibit tumour cell growth and enhance apoptosis in human colon cancer cells. However, it is suggested that RYR may have anticancer activity, additional to those conferred by its statin content, as lovastatin-induced tumour inhibition was found to be reversed by mevalonate while RYR-induced inhibition was not. This has led to the suggestion that other components in RYR, including other monacolins, pigments or the combined matrix effects of multiple constituents, may affect intracellular signalling pathways differently from lovastatin (Hong et al 2008a, 2008b) This suggestion is supported by a study on prostate cancer cells, which found that RYR showed a more potent inhibition effect on prostate cancer cell growth compared to lovastatin (Hong et al 2008b).

Osteogenesis

Statins have recently been shown to stimulate bone formation and RYR preparations have also been shown to produce strong bone anabolic effects, both in vitro and in vivo (Gutierrez et al 2006, Wong & Rabie 2008). The ability of flavonoids and statins that occur naturally in food products to promote bone formation has led to the suggestion that RYR may provide a dietary intervention to stimulate bone formation and prevent osteoporosis (Mundy 2006).

Antidiabetic

Oral administration of RYR decreased plasma glucose and delayed the development of insulin resistance in rats fed a fructose-rich diet, as well as improved insulin sensitivity in streptozotocin-induced diabetic rats (Su et al 2007). RYR has also been shown to attenuate the elevation of plasma glucose induced by an intravenous glucose challenge test in normal rats and reverse hyperphagia in streptozotocin-diabetic rats (Chang et al 2006). Further rat studies suggest that the plasma glucose-lowering action of RYR is due to release of acetylcholine and subsequent stimulation of muscarinic M3 receptors in pancreatic cells that effect insulin release (Chen & Liu 2006) as well as decrease hepatic gluconeogenesis to lower plasma glucose in diabetic rats lacking insulin (Chang et al 2006).

CLINICAL USE

Hyperlipidaemia

In addition to empirical use over hundreds of years attesting to its safety and efficacy, there are at least 100 randomised controlled trials of RYR products. A recent meta-analysis of 93 RCTs on three RYR preparations (Cholestin, Xuezhikang and Zhibituo), which included 9625 participants, found significant reduction of serum total cholesterol levels, triglycerides levels and LDL cholesterol levels, and increase of HDL cholesterol levels with RYR supplementation compared with placebo. These studies found that the lipid modification effects of RYR are similar to that of statin medications and that RYR was generally safe and well tolerated. When compared with non-statin lipid-lowering agents, RYR preparations appeared superior to nicotinate and fish oils, but equal to or less effective than fenofibrate and gemfibrozil (Liu et al 2006).

A multicentre, placebo-controlled trial of a partially purified extract of red yeast rice (Xuezhikang), involving 4870 patients, found that 4.5 years of

supplementation lowered total and low-density lipoprotein cholesterol and triglycerides, and raised high-density lipoprotein cholesterol levels. This study also found a relative risk reduction of 45% and an absolute risk reduction of 4.7% for coronary events, along with a 33% reduction in total mortality in those taking the RYR extract. Interestingly, this study also found a marked 45% reduction of cancer-related deaths (Lu et al 2008). A substudy involving 591 diabetic patients from the same group found even more dramatic results with a 50% reduction in cardiovascular events and a 44% reduction in overall mortality in the patients taking RYR compared to those taking placebo (Zhao et al 2007).

In a small randomised, double-blind, placebo-controlled pilot study involving 14 adults with dyslipidaemia related to HIV, RYR supplementation for 8 weeks was found to lower total and low-density lipoprotein cholesterol without any adverse effects (Keithley et al 2002).

OTHER USES

It has been suggested that in addition to reducing cholesterol, it is possible that monacolins could prevent stroke and reduce the development of peripheral vascular disease. This class of molecules have antithrombotic and anti-inflammatory effects, which may offer protection against atherosclerotic plaque growth as well as being used for the treatment of hypertension, osteoporotic fractures, ventricular arrhythmia and immune response (Manzoni & Rollini 2002).

DOSAGE RANGE

RYR is a dietary staple in many Asian countries with typical consumption ranging from 14–55 g/person/day. The average dose of RYR products is 2.4 g/day depending on the product used.

ADVERSE REACTIONS

The recent meta-analysis revealed that, of the 77 controlled trials that reported adverse events, there were no serious adverse events reported, while non-serious adverse effects were limited to dizziness, low appetite, nausea, stomach ache, abdominal distention and diarrhoea, with a small proportion of participants having increased serum blood urea nitrogen and alanine aminotransferase levels (ALT) (Liu et al 2006).

The American College of Cardiology Task Force on integrating complementary medicine into cardiovascular medicine suggested that RYR should be 'treated as an HMG-CoA reductase inhibitor, with all the possible side effects, drug interactions, and precautions associated with this class of drugs' (Vogel et al 2005). While the statin drugs are used extensively throughout the world and are generally recognised as safe, they have the potential to reduce endogenous production of CoQ10 and cause rhabdomyolysis.

A number of cases of statin-like muscle damage that may be related to very low CoQ10 levels have been reported in patients taking red yeast rice (Smith & Olive 2003, Vercelli et al 2006), and animal studies have demonstrated a dose-dependent reduction in CoQ10 levels with high levels of RYR (Yang et al 2005).

SIGNIFICANT INTERACTIONS

Statin drugs

RYR products contain low doses of natural statins and, as such, a pharmacodynamic interaction is possible with other statin medications.

Cyclosporin and P450 inhibitors

Monacolins are metabolised by the cytochrome P450 system and therefore cyclosporin and other P450 inhibitors have the potential to increase the risk of rhabdomyolysis (Prasad et al 2002).

Coenzyme Q10

Similar to statin medications, RYR may reduce endogenous production of CoQ10 — concurrent supplementation with CoQ10 may be worth considering with long-term use of RYR.

CONTRAINDICATIONS AND PRECAUTIONS

Patients with statin-induced muscle damage should be advised against using RYR (Vercelli et al 2006).

PREGNANCY USE

Insufficient reliable information is available to confirm safety in pregnancy. Safety unknown.

PRACTICE POINTS/PATIENT COUNSELLING

- RYR is a complex whole food substance that has long traditional use as a food and medicine and is still a common feature of Asian diets.
- RYR has been found to contain monacolins (statins) which are used to lower cholesterol and reduce the risk of cardiovascular disease. RYR may also have anti-inflammatory, anti-cancer and bone-forming properties.
- There are differences between different RYR products, some of which are standardised to statin content.
- RYR products should be stored away from heat and light.

PATIENTS' FAQs

What will this supplement do for me?

RYR can be used to lower cholesterol levels and reduce the risk of atherosclerosis. It may also have beneficial effects for people with diabetes, osteoporosis, inflammatory disease and cancer.

When will it start to work?

Effects may be noticed immediately with full cholesterol lowering effects being evident after 6–8 weeks.

Are there any safety issues?

RYR may have rare adverse effects similar to the statin medications, such as unexplained muscle pain and weakness that can lead to kidney damage.

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Rhodiola

HISTORICAL NOTE Rhodiola is a popular herb in the traditional medicine of Eastern Europe, Asia and Scandinavia where it has been used to stimulate the nervous system, enhance physical and mental performance and improve resistance to high-altitude sickness (van Diermen et al 2009). It grows in high-altitude Arctic regions of Europe and Asia (Goel et al 2006) and is reported to have been used by the Vikings to enhance physical strength and endurance (Darbinyan et al 2007). It is also mentioned by Dioscorides as early as the first century AD. Rhodiola has been categorised as an 'adaptogen' in traditional systems due to its ability to increase resistance to a variety of chemical, biological and physical stressors; and is noted for its antidepressant, anticancer and cardioprotective properties (Kelly 2001). It has a reputation for improving depression, enhancing work performance, eliminating fatigue and treating symptoms of debility following intense physical and psychological stress (Perfumi & Mattioli 2007).

OTHER NAMES

Arctic root, golden root, Hongjingtian, king's crown, Lignum rhodium, rose root, Russian rhodiola, Siberian golden root

BOTANICAL NAME/FAMILY

Rhodiola rosea (family Crassulaceae)

A number of rhodiola species can be identified in the scientific literature and may possess varying pharmacological activities, chemical constituents and efficacy in clinical application (Kucinskaite et al 2007, Li & Zhang 2008). These include: the Indian herb *rhodiola imbricata* (Goel et al 2006) and the Tibetan herb *rhodiola sacra* (Shih et al 2008), *rhodiola quadrifida* (Skopnska-Rozewska et al 2008), *rhodiola sachalinensis* (Wu et al 2008), *rhodiola crenulata* (Song et al 2008) and *rhodiola dumulosa* (Liu et al 2008).

PLANT PART USED

Root

CHEMICAL COMPONENTS

Salidroside (aka rhodiolosides A-F; monoterpene glycosides), and their aglycones; rhodiolol A, rosiridol and sachalinol A (Ali et al 2008, Li W et al 2008, Li HB et al 2008, Ma et al 2006, Yu et al 2008); rosavins (rasavin, rosin, rosarin; phenylpropanoids) (Kucinskaite et al 2007); gossypetin-7-O-L-rhamnopyranoside, rhodioflavonoside, gallic acid, trans-p-hydroxycinnamic acid and p-tyrosol (Ming et al 2005); cinnamic alcohol, cinnamaldehyde and cinnamic acid (Panossian et al 2008); hydroquinone (Wang et al 2007). The balance of rosavins to salidrosides is usually 3:1.

MAIN ACTIONS

Adaptogenic (modulates stress response)

Prolonged exposure to stressful life events and depression may contribute to significant behavioural, endocrinological and neurobiological changes in both humans and animals. Animal studies have suggested that chronic administration of rhodiola extract (standardised to 3% rosavin and 1% salidroside; 10, 15 and 20 mg/kg by gavage) results in potent inhibition of the behavioural and physiological changes induced by chronic exposure to mild stressors in a manner comparable to those of fluoxetine (oral 10 mg/kg) (Mattioli et al 2009). Other studies suggest an ability to selectively attenuate stress-induced anorexia (Mattioli & Perfumi 2007). In experimental studies, extracts of rhodiola appear to increase stress resistance and contribute to a longer lifespan. The extract induces translocation of the DAF-16 transcription factor from the cytoplasm into the nucleus, suggesting a reprogramming of transcriptional activities favouring the synthesis of proteins involved in stress resistance and longevity (Wiegant et al 2009).

Single-dose studies of rhodiola extract (standardised to 3% rosavin and 1% salidroside; 10, 15 and 20 mg/kg) have demonstrated antidepressant, adaptogenic, anxiolytic and stimulating effects in mice (Perfumi & Mattioli 2007). In addition, rhodiola has been reported to prevent catecholamine release and subsequent cyclic AMP elevation in the myocardium, and the depletion of adrenal catecholamines induced by acute stress in vivo (Maslova et al 1994). According to Panossian (2005), the beneficial effects of multidose administration of adaptogens, such as rhodiola, are mainly associated with the hypothalamic–pituitary–adrenal (HPA) axis, while single-dose applications are more useful in situations that require a rapid response to tension or to a stressful situation via the sympatho-adrenal-system (SAS). Rhodiola exerts a stimulating effect within 30 min of administration that continues for approximately 4–6 h. This activity appears to be due to salidroside and rosavin (Panossian & Wagner 2005).

Improved physical performance

While earlier animal studies seemed promising (Abidov et al 2003, Azizov & Seifulla 1998), rhodiola has produced mixed results when attempting to demonstrate an ergogenic effect during exercise in humans (Walker & Robergs 2006). Rhodiola is purported to enhance physical performance, possibly by improving adenosine triphosphate (ATP) turnover; however, several small-scale human trials have failed to confirm these effects. In a placebo-controlled trial 12 resistance-trained men received rhodiola (1500 mg/day) or placebo for 4 days. After completing incremental forearm wrist flexion exercise to volitional fatigue no significant improvements were demonstrated for time to exhaustion or recovery (Walker et al 2007). A combination formula containing rhodiola also failed to demonstrate significant effects on muscle tissue oxygen saturation, $VO_{2max,}$ ventilatory threshold or time to exhaustion in a placebo-controlled study involving eight participants (Colson et al 2005). Single-dose administration of rhodiola extract (200 mg standardised to 3% rosavin and 1% salidroside) may prove to be more promising with earlier studies showing benefits in time to exhaustion (16.8 ± 0.7 min to 17.2 ± 0.8 min; $P < 0.05$), VO_{2peak} and $VCO_{2peak,}$ and also possibly pulmonary ventilation ($P = 0.07$) (124.8 ± 7.7 L/min versus 115.9 ± 7.7 L/min) (De Bock et al 2004). Rhodiola also exhibits anti-inflammatory activity and protects muscle tissue from damage during exercise according to a study involving healthy untrained volunteers who performed exhausting exercise (Abidov et al 2004).

Improved mental performance

It has been suggested that rhodiola extract promotes the release of monoamine neurotransmitters in the ascending pathways of the brainstem thus activating the cerebral cortex and limbic system. As a result, cognitive function, attention, memory and learning may be enhanced (Panossian & Wagner 2005). Animal experiments have demonstrated improvements in learning and retention after 24 h following a single dose (0.10 mL/rat) and long-term memory after 10 days treatment at the same dose. Higher (1.0 mL) and lower (0.02 mL) doses did not appear to be effective (Petkov et al 1986).

In the 1960s, Zatova demonstrated that a single dose of *R. rosea* extract could improve mental performance. Eighty-five healthy males and females, aged 20–28 years old working under the same conditions, were studied using Anfimov's table (which provides numerically comparable data characterising the quality and quantity of work performed). Doses of 5–10 drops were found to be the most effective, reducing the number of errors by an average of 46%. At a dose of five drops, the rhodiola extract led to a reduction in the number of errors in 88% of the subjects tested, but to an increase in the remaining 12%; in comparison to placebo which produced a reduction in the number of errors in 35% of the subjects, an increase in 58% and no change in the remaining 7% (Panossian & Wagner 2005).

During a 12-week study, the efficacy and safety of rhodiola extract given in combination with vitamins and minerals (vigodana®) was tested in 120 adults (83 women and 37 men, aged 50–89 years) with physical and cognitive deficiencies (Fintelmann & Gruenwald 2007). Two different dosage regimens were chosen: 2 capsules orally in the morning after breakfast, or 1 capsule after breakfast and 1 after lunch. A statistically significant improvement ($P < 0.001$) in physical and cognitive performance was observed in both groups but was more pronounced in the group taking both capsules after breakfast. No adverse events occurred during the course of the study (Fintelmann & _Gruenwald 2007). While the results of this study are promising, they need to be confirmed by more rigorously designed placebo-controlled clinical trials of rhodiola alone.

Anticholinesterase

Spectral methods (NMR, UV and MS) have identified a strong anticholinesterase activity for hydroquinone, a component of rhodiola (Wang et al 2007).

Antidepressant

Rhodiola is one of the more promising herbal medicines for the treatment of monopolar depression (Kelly 2001, Kucinskaite et al 2004, Sarris 2007). It appears to influence the levels and activity of monoamine neurotransmitters such as serotonin, noradrenalin and dopamine (Stancheva & Mosharrof 1987). Recently, extracts of rhodiola exhibited potent anti-depressant activity by inhibiting monoamine oxidase (MAO)-A in vitro which may partly explain its effects (van Diermen et al 2009). It is suspected that rhodiola also facilitates neurotransmitter transport within the brain (Stancheva & Mosharrof 1987). Other studies indicate that antidepressant effects are likely due to salidroside on stress-activated protein kinases (SAPK), which play a key role in HPA axis overactivity by inhibiting the sensitivity of glucocorticoid receptors to cortisol (Darbinyan et al 2007).

Immunomodulation

While studies using rhodiola alone for immune modulation could not be located, several polyherbal preparations containing rhodiola have been tested producing good results. In a placebo-controlled trial, a combined preparation known as Admax® (Nulab Inc) containing *rhodiola rosea* in combination with *Eleutherococcus senticosus*, *Schisandra chinensis* and *Leuzea carthamoides* (270 mg/day) was given to 28 patients with stage III–IV epithelial ovarian cancer receiving a one-off dose of cisplatin (75 mg/m^2) and cyclophosphamide (600 mg/m^2). Subjects received treatment or placebo for 4 weeks. In patients who took Admax, the mean numbers of four T cell subclasses (CD3, CD4, CD5 and CD8) and the mean amounts of IgG and IgM were increased suggesting attenuation of the suppressed immunity experienced by ovarian cancer patients undertaking chemotherapy (Kormosh et al 2006). Additionally, a double-blind, placebo-controlled, randomised trial of Chisan® (a standardised combination of *rhodiola rosea*, *Schisandra chinensis* and *Eleutherococcus senticosus*) was carried out on 60 patients receiving cephazoline, bromhexine and theophylline for acute non-specific pneumonia. The addition of Chisan twice daily for 10–15 days in the treatment group resulted in a 2-day reduction in the mean time required to bring about recovery from the acute phase and improved quality-of-life (QOL) scores during convalescence (Narimanian et al 2005).

Antibacterial

The methanolic extract of rhodiola root has been shown to inhibit the activity of *Staphylococcus aureus* in Microbial Sensitivity Tests. The active compounds were identified as gossypetin-7-O-L-rhamnopyranoside and rhodioflavonoside at concentrations of 50 microgram/mL and 100 microgram/mL, respectively (Ming et al 2005).

Cardioprotective

Rhodiola extract has been shown to exert cardioprotective effects in vivo. More specifically, rhodiola extract demonstrates protection against reperfusion injury after ischaemia, antiarrhythmic activity and increases serum levels of beta-endorphin and leu-enkephalin in myocardial tissue. The effects appear to be dependent on the occupancy of opioid receptors by endogenous opioid peptides (Maslov & Lishmanov 2007). Oral administration of rhodiola rosea extract (3.5 mg/kg) also appears to have a favourable effect on heart contractility and coronary flow parameters due to an increase in the level of endogenous opioid peptides (Lishmanov et al 1997). The anti-arrhythmic effect of rhodiola extract is a result of activation of both central and peripheral opioid receptors (Maimeskulova & Maslov 2000) and stimulation of kappa-OR (Maimeskulova et al 1997). It is suspected that herbal treatment increases endogenous production of opioids.

Combination preparations, such as tonizid (containing *rhodiola rosea* in combination with *Aralia mandshurica*, *Panax ginseng* and *Eleutherococcus senticosus*), have also demonstrated cardioprotective and antifibrillatory properties during acute cardiac ischaemia/reperfusion and postinfarction cardiac fibrosis (Arbuzov et al 2006, Lishmanov et al 2008).

OTHER ACTIONS

Antioxidant

Rhodiola extract reduces oxidative stress in vitro (Battistelli et al 2005) and increases endogenous antioxidant production in vivo. Rhodiola was able to significantly protect human erythrocytes from glutathione (GSH) depletion, glyceraldehyde-3-phosphate dehydrogenase (GAPDH) inactivation and haemolysis induced by the oxidant hypochlorous acid (HOCl), in a dose-dependent manner (De Sanctis et al 2004). In animal studies, rhodiola extract (200 mg/kg/day for 12 weeks) increased the levels of reduced glutathione and the activity of glutathione reductase, glutathione S-transferase, glutathione peroxidase, catalase and superoxide dismutase in the liver (Kim et al 2006). In human trials, a trend towards decreased lipid peroxidation has been observed following 7-day treatment with rhodiola rosea (Wing et al 2003).

Antidiabetic

Rhodiola extract (200 mg/kg/day for 12 weeks) significantly decreases blood glucose and lipid peroxidation in vivo. It also increases levels of reduced glutathione and the activity of glutathione reductase, glutathione S-transferase, glutathione peroxidase, catalase and superoxide dismutase in the liver (Kim et al 2006). Further in vivo studies have revealed that water-soluble rhodiola extract inhibits alpha-glucosidase and pancreatic alpha-amylase (Apostolidis et al 2006). Ethanolic extracts also inhibit alpha-amylase, alpha-glucosidase and also angiotensin-converting enzyme (ACE) (Kwon et al 2006). The effect appears to be dependent on the phenolic content and profile (Apostolidis et al 2006, Kwon et al 2006). In experimental studies, salidroside, one of the major active components of rhodiola, has a dose-dependent effect on glucose transport activation and insulin sensitivity via AMP-activated protein kinase (AMPK) activation (Li HB et al 2008) and may inhibit lipid peroxidation (Zhang & Liu 2005).

Neuroprotective

Salidroside, an isolated component of rhodiola, has demonstrated a dose-dependent neuroprotective effect in animal models (Bocharov et al 2008). Salidroside has protective effects against oxidative stress-induced cell apoptosis (Zhang et al 2007), inhibits intracellular reactive oxygen species (ROS) production and restores mitochondrial membrane potential (Yu et al 2008) and decreases intracellular free calcium concentration (Zhang et al 2004). As a result, salidroside may warrant further investigation for preventing and treating cerebral ischaemic and neurodegenerative diseases (Yu et al 2008).

Ctyoprotective

Salidroside, extracted from *rhodiola rosea*, may protect PC12 cells against glutamate excitotoxic damage through suppressing the excessive entry of calcium and the release of the calcium stores (Cao et al 2006).

Hepatoprotective

Hepatoprotective effects have been demonstrated in rats with experimental toxic hepatitis: normalising the activity of aspartate aminotransferase (AST) and alkaline phosphatase (ALP); reducing the activity of alanine aminotransferase (ALT) and glutathione-S-transferase; and normalising the content of medium-molecular-weight peptides, urea and bilirubin in plasma (Iaremii & Grigor'eva 2002). Rhodiola extract has also been shown to reduce the liver dysfunction associated with adriamycin (an anthracycline antibiotic) in mice without affecting the drug's antitumour activity (Udintsev et al 1992).

Anticancer effects (antimutagenic, cytostatic, antiproliferative, antimetastatic)

Rhodiola extract seems to have anticancer activity according to test tube and animal studies, which is due to a combination of mechanisms. rhodiola rosea extracts reduce experimentally induced mutations, most likely due to increased efficiency of intracellular DNA repair mechanisms (Salikhova et al 1997). The cytostatic and antiproliferative effects of rhodiola extract have been demonstrated in experimental models. Rhodiola has been shown to inhibit the division of HL-60 cells leading to induction of apoptosis and necrosis, and to a marked reduction in their survival. After treatment with the extract, no chromosome aberrations or micronuclei were observed (Majewska et al 2006). Antiproliferative and antimetastatic effects have been noted in animal models of Pliss lymphosarcoma (Udintsev & Shakhov 1991b). A decrease of cyclophosphamide haematotoxicity by rhodiola rosea root extract in mice with Ehrlich and Lewis transplantable tumours has also been demonstrated (Udintsev & Schakhov 1991a).

In a small human trial, oral administration of rhodiola extract to 12 patients with superficial bladder carcinoma (T1G1-2) resulted in improvements in urothelial tissue integration, parameters of leukocyte integrins and T-cell immunity. A non-significant reduction in the average frequency of relapse was also noted (Bocharova et al 1995).

CLINICAL USE

Stress and fatigue

Three double-blind studies indicate that treatment with rhodiola extract (SHR-5) has significant antifatigue effects, whereas one study was inconclusive. The most studied extract to date for these indications is SHR-5.

A 28-day course of rhodiola extract SHR-5 (576 mg extract/day) demonstrated a significant antifatigue effect that increases mental performance, particularly the ability to concentrate, and decreases cortisol response to awakening stress in burnout patients with fatigue syndrome (Olsson et al 2008). The randomised, double-blind, placebo-controlled study involved 60 volunteers aged between 20 and 55 years with fatigue syndrome who were randomised to receive four tablets daily of SHR-5 extract (576 mg extract/day) or four placebo tablets daily. Previously, in a randomised, double-blind, placebo-controlled, parallel-group

study, single doses of standardised rhodiola extract (SHR-5) were administered to 161 cadets aged 19–21 years. A highly significant antifatigue effect using the antifatigue index (AFI) was demonstrated for both standard (9 mg/day salidroside) and high dose (13.5 mg/day salidroside) regimens (Shevtsov et al 2003). Repeated low-dose treatment of the standardised extract SHR-5 (standardised to 4.5 mg/day of salidroside) was also tested in a double-blind, crossover trial of 56 young, healthy doctors during night duty. The study also demonstrated a statistically significant antifatigue effect resulting in improvements in the overall level of mental fatigue, concentration and speed of audio–visual perception during the first 2-week period of the crossover study. Following a 2-week washout period, the second treatment group did not experience the same benefits which may have been due to them having been on night duty for a longer period (Darbinyan et al 2000). The same extract (SHR-5) was also used in a double-blind, randomised, placebo-controlled trial of foreign students during a stressful examination period. A repeated low-dose regimen was administered for 20 days resulting in significant improvements in physical fitness, mental fatigue and neuro-motoric tests ($P < 0.01$). Average examination results were also higher in the treatment group (Spasov et al 2000).

Depression

Several studies with experimental models have shown that rhodiola exhibits significant antidepressant activity and in vitro tests provide plausible mechanisms of action (Panossian & Wagner 2005, Perfumi & Mattioli 2007). In one study, rhodiola exhibited a stronger antidepressant effect than either imipramine (30 mg/kg) or *Hypericum perforatum* (20 mg/kg). Rhodioloside and tyrosol were identified as active principles (Panossian et al 2008). Despite this encouraging preliminary evidence, clinical investigation has only just begun.

In a randomised, double-blind, placebo-controlled study with parallel groups conducted over 6 weeks, 89 participants, male and female, aged 18–70 years were selected according to Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV diagnostic criteria for mild-to-moderate depression (Darbinyan et al 2007). The severity of the depression was determined by scores gained in the Beck Depression Inventory (BDI) and Hamilton Rating Scale for Depression (HAMD) questionnaires. Patients with initial HAMD scores between 21 and 31 were randomised to receive either rhodiola rosea extract SHR-5 (340 mg/day) or SHR-5 (680 mg/day) or placebo. At the end of the 6-week trial, participants in both treatment groups experienced significant improvements ($P < 0.0001$) in overall depression, insomnia, emotional instability and somatisation compared to the placebo group. The high-dose group also experienced improvements in self-esteem. There was a dose-dependent effect for the BDI but not for the HAMD and no serious side effects were reported in any of the groups (Darbinyan et al 2007). As a result, rhodiola may represent a useful therapy for the treatment of depression due to glucocorticoid resistance following stressful life events and may be a safer alternative to St John's wort with its potential drug interactions.

Generalised anxiety disorder

In a small pilot study, 10 participants aged 34–55 years were selected according to DSM-IV diagnostic criteria for generalised anxiety disorder (GAD). Participants received rhodiola extract (340 mg/day) for 10 weeks after which time there was a significant decrease in mean Hamilton Anxiety Rating Scale (HARS) scores. Only mild-to-moderate adverse effects were noted, most commonly dizziness and dry mouth, and no drug interaction was observed in the three patients taking benzodiazepines (Bystritsky et al 2008). Larger well-designed trials should be conducted to confirm these effects.

Improved physical performance

There is conflicting evidence on the effect of roseroot for improving athletic performance. While earlier animal studies seemed promising (Abidov et al 2003, Azizov & Seifulla 1998), rhodiola has produced mixed results when attempting to demonstrate an ergogenic effect during exercise in humans (Walker & Robergs 2006).

In a placebo-controlled trial, 12 resistance-trained men, aged 19–39 years, completed an incremental forearm wrist flexion exercise to fatigue, after ingesting rhodiola (1500 mg/day) or placebo for 4 days. There were no significant differences between groups for time to exhaustion or recovery (Walker et al 2007). Similarly, a double-blind, randomised, placebo-controlled trial of a traditional Chinese medicine combination containing *rhodiola rosea* and *Cordyceps sinensis* also failed to demonstrate significant effects on muscle tissue oxygen saturation, VO_{2max}, ventilatory threshold or time to exhaustion (Colson et al 2005).

Conversely, an earlier double-blind, placebo-controlled study had demonstrated beneficial effects with acute but not with chronic dosing of rhodiola. A single dose of rhodiola extract (200 mg standardised to 3% rosavin and 1% salidroside) significantly increased time to exhaustion (16.8 ± 0.7 min to 17.2 ± 0.8 min; $P < 0.05$), VO_{2peak} and VCO_{2peak} compared to placebo, and also tended to increase pulmonary ventilation ($P = 0.07$) (124.8 ± 7.7 L/min versus 115.9 ± 7.7 L/min). Prior administration of the same dose daily for 4 weeks did not alter any of the variables measured (De Bock et al 2004). rhodiola has also been shown to exhibit an anti-inflammatory effect and protect muscle tissue during exercise in healthy untrained volunteers before and after exhausting exercise (Abidov et al 2004).

OTHER USES

Reward deficiency syndrome (RDS)

Reward deficiency syndrome (RDS), associated with low dopamine 2 (D2) receptors, may increase craving behaviour causing the individual to seek out substances that increase the release of dopamine. Researchers in this area have suggested that the addition of rhodiola, a known

catechol-O-methyl-transferase (COMT) inhibitor, may be a useful adjunct to the treatment of this condition. It is thought that during recovery or rehabilitation from alcohol or other psychoactive drugs (dopamine releasers), decreasing COMT activity should result in 'enhanced synaptic dopamine, thereby proliferating D2 receptors while reducing stress, increasing wellbeing, reducing craving behaviour and preventing relapse' (Blum et al 2007).

Cardiovascular disease prevention

In animal studies, rhodiola extract has demonstrated cardioprotective, antiarrhythmic and antioxidant effects (Lishmanov et al 1997, Maimeskulova & Maslov 2000, Maslov & Lishmanov 2007, Wing et al 2003). Further research is warranted to investigate whether these effects are clinically relevant in human populations at risk of cardiovascular disease.

Diabetes

In animal studies, rhodiola extract (200 mg/kg/day for 12 weeks) significantly decreased blood glucose and lipid peroxidation. It also increased the levels of reduced glutathione and the activities of glutathione reductase, glutathione S-transferase, glutathione peroxidase, catalase and superoxide dismutase in the liver. As increased oxidative stress has been shown to play an important role in the pathogenesis and long-term complications of diabetes mellitus, this herb warrants further investigation (Kim et al 2006).

DOSAGE RANGE

- Fluid extract (1:2): 20–40 mL/wk (Australian manufacturer recommendations).
- In clinical trials, extracts are often standardised to 3% rosavin and 1% salidroside (Perfumi & Mattioli 2007).
- Stress and fatigue: one-off acute dosing (equiv 9 mg/day–13.5 mg/day salidroside) (Shevtsov et al 2003); repeated low-dose treatment (eqiv. 4.5 mg/day of salidroside) (Darbinyan et al 2000).
- Depression and anxiety: rhodiola extract 340 mg/day (equiv 1500 mg dried root) (Bystritsky et al 2008, Darbinyan et al 2007).

Note: One study suggested improved results from taking rhodiola after breakfast rather than in divided doses after breakfast and lunch (Fintelmann & Gruenwald 2007). This may be due to diurnal variations in HPA and adrenal function.

ADVERSE REACTIONS

Serious adverse effects have not been reported in clinical trials; however, mild-to-moderate symptoms of dizziness and dry mouth have been noted (Bystritsky et al 2008).

SIGNIFICANT INTERACTIONS

As controlled studies are not available, interactions are currently speculative and based on evidence of pharmacological activity and animal studies.

Adriamycin

Rhodiola extract has been shown to reduce the liver dysfunction (suggested by a sharp increase in blood transaminase levels) associated with adriamycin in vivo without affecting the drug's antitumour effects (Udintsev et al 1992). Beneficial interaction possible under clinical supervision.

Cyclophosphamide

In animal tumour models (Ehrlich ascites tumour and Lewis lung carcinoma), the combination of rhodiola rosea extract with cyclophosphamide resulted in enhanced antitumour and antimetastatic activities and reduced drug-induced toxicity on bone marrow cells (Razina et al 2000, Udintsev & Schakhov 1991b). Beneficial interaction possible under clinical supervision.

Antidepressants

As recent in vitro data suggests an inhibition of MAO A by rhodiola extracts (van Diermen et al 2009), a theoretical interaction exists with MAOI antidepressants. The clinical significance of this and whether other antidepressants may be affected is as yet unclear. Observe.

CONTRAINDICATIONS AND PRECAUTIONS

While the administration of rhodiola may be beneficial in monopolar depression, use is not recommended for bipolar states.

Theoretically, the possibility of the herb exerting MAO inhibiting effects may require consumers to adhere to dietary restriction of tyramine-rich foods (e.g. some cheeses, pickled foods, chocolates, meats, beer, wine etc), as the interaction of tyramine with MAOIs can result in a significant elevation in blood pressure.

PREGNANCY USE

Safety in pregnancy and lactation has not been established.

PRACTICE POINTS/PATIENT COUNSELLING

- Rhodiola may exert an antidepressant effect via the inhibition of MAO A; inhibiting the sensitivity of glucocorticoid receptors to cortisol (induced by stress) or by facilitating neurotransmitter transport within the brain.
- Some studies suggest that extracts of rhodiola may increase stress resistance, improve fatigue and reduce anxiety.
- Multidose administration of rhodiola may influence the hypothalamic–pituitary–adrenal (HPA) axis, while single-dose applications are more useful in situations that require a rapid response to tension or to a stressful situation via the sympatho-adrenal-system (SAS).
- Animal studies show possible benefits in cardiovascular disease and diabetes, which may relate to its antioxidant effects.
- Limited trials in humans have failed to demonstrate significant benefits for enhancing physical performance.
- Many trials use rhodiola in combination with other herbs or nutrients making it difficult to ascertain the pharmacological and clinical effects of the individual herb.

PATIENTS' FAQs

What will this herb do for me?

Rhodiola may be of assistance in the treatment of stress-related conditions, in particular depression and fatigue.

When will it start to work?

Rhodiola exerts a stimulating effect within 30 min of administration that continues for approximately 4–6 h.

In mild-to-moderate depression, the benefits of rhodiola rosea extract SHR-5 (340 mg/day) or SHR-5 (680 mg/day) were noted at the end of a 6-week trial.

Are there any safety issues?

Mild-to-moderate symptoms of dizziness and dry mouth have been noted in clinical trials and patients taking MAOI antidepressants may need consideration until more is known about the mechanism of action of this herb. Safety in pregnancy and lactation has not been established.

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Rosemary

HISTORICAL NOTE Since ancient times, rosemary has been used as a tonic and stimulant. The ancient Greeks used it to strengthen memory function and scholars wore garlands of rosemary during examinations in order to improve their memory and concentration (Blumenthal et al 2000). It is widely used as a food spice and as an antioxidant to preserve foods.

COMMON NAME
Rosemary

OTHER NAMES
Compass plant, compass weed, garden rosemary, old man, polar plant, *Rosmarini folium*

BOTANICAL NAME/FAMILY
Rosmarinus officinalis (family Labiatae or Lamiaceae)

PLANT PART USED
Fresh or dried leaf

CHEMICAL COMPONENTS
Phenolic acids and diterpenoid bitter substances, including carnosic acid and carnosol (Aruoma et al 1992, Bicchi et al 2000, Wei & Ho 2006), triterpenoid acids, flavonoids, tannins and volatile oils (0.5–2.5%) that consist of 1,8-cineole, 2-ethyl-4,5-dimethylphenol gamma-terpinene (Kabouche et al 2005), pinene, terpineol, camphor, camphene, borneol and bornyl acetate (Blumenthal et al 2000). Rosemary has also been found to contain high amounts of salicylates (Swain et al 1985).

MAIN ACTIONS

Antioxidant

Rosemary has strong antioxidant activity and is widely used to preserve food and cosmetics (Etter 2004). Rosemary leaf extract has been shown to enhance superoxide dismutase activity (Kim et al 1995) and to have an effect stronger than vitamin E in scavenging oxygen radicals (Zhao et al 1989). It is suggested that carnosol and carnosic acid account for over 90% of its antioxidant properties (Aruoma et al 1992, 1996). Carnosic acid has been shown to have a photoprotective action on human dermal fibroblasts exposed to UVA light in vitro (Offord et al 2002) and rosemary extract inhibits oxidative alterations to skin surface lipids, both in vitro and in vivo (Calabrese et al 2000), as well as enhancing cell-mediated immunity in rats under oxidative stress (Babu et al 1999). In a study of 150 patients with bronchitis exposed to essential oils of rosemary, basil, fir and eucalyptus, an antioxidant effect was observed (Siurin 1997).

Antibacterial

Rosemary extract demonstrates in vitro antibacterial activity against a variety of bacteria (Del Campo et al 2000, Erdogrul 2002, Ouattara et al 1997), including *Helicobacter pylori* (Mahady et al 2005), *Staphylococcus aureus* (Oluwatuyi et al 2004), *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* (Kabouche et al 2005). Topical application of rosemary essential oil preparations has been found to have antifungal activity (Ouraini et al 2005, Steinmetz et al 1988, Suleimanova et al 1995) and to inhibit the growth and aflatoxin production of *Aspergillus* spp at concentrations between 0.2% and 1% (Tantaoui-Elaraki & Beraoud 1994). Carnosol has been found to have anti-HIV activity (Aruoma et al 1996) and carnosic acid has also been shown to have an inhibitory effect on HIV-1 protease in cell-free assays (Paris et al 1993). Rosemary extract has some antiviral activity against HSV (Vijayan et al 2004). Powdered rosemary leaves are said to be effective as a natural flea and tick repellent and rosemary essential oil has been found to be ovicidal and repellent towards mosquito (Prajapati et al 2005).

Anti-inflammatory

In vitro studies have found that rosemary extracts inhibited inflammatory-induced peroxynitrite radical and nitrite production (Chan et al 1995, Choi et al 2002) and that carnosol suppresses NO production (Lo et al 2002). Rosmarinic acid has been found to increase the production of PGE_2, reduce the production of leukotriene B_4 in human polymorphonuclear leucocytes, and inhibit the complement system (al-Sereiti et al 1999).

Hepatoprotective

The hepatoprotective properties of rosemary extract are attributed to its antioxidant properties and improving detoxification systems dependent on glutathione S-transferase (Sotelo-Felix et al 2002). Rosemary extract has been shown to reduce thioacetamide-induced cirrhosis (Galisteo et al 2000) and azathioprine-induced toxicity in rats (Amin & Hamza 2005), as well as partially prevent carbon tetrachloride-induced liver damage in both rats (Sotelo-Felix et al 2002) and mice (Fahim et al 1999, Sotelo-Felix et al 2002).

Chemoprotection and antimutagenic effects

In vivo studies suggest that rosemary extract may reduce the effects of carcinogenic or toxic agents on many cell lines, including rat mammary gland (Amagase et al 1996, Singletary et al 1996), mouse liver and stomach (Singletary & Rokusek 1997), bone marrow (Fahim et al 1999) and skin (Huang et al 1994).

An in vitro study on human bronchial cells found that rosemary extract and its constituents, carnosol and carnosic acid, may have chemoprotective activity by decreasing carcinogen activation via inhibition of the enzyme cytochrome P450 (CYP1A1) and increasing carcinogen detoxification by induction of phase II enzymes (Offord et al 1995). Carnosol has been found to also restrict the invasive ability of mouse melanoma cells in vitro by reducing MMP-9 expression and activity (Huang et al 2005).

Increases oestrogen metabolism

Feeding female mice a 2% rosemary diet enhanced the liver microsomal metabolism of endogenous oestrogens (Zhu et al 1998), thereby reducing oestrogen levels.

OTHER ACTIONS

Carnosic acid and carnosol, which are major components of rosemary, have been found to markedly enhance synthesis of nerve growth factor in vitro (Kosaka & Yokoi 2003). Rosemary has been also demonstrated to have significant antithrombotic activity in vitro and in vivo, possibly through a direct inhibitory effect on platelets (Yamamoto et al 2005). Rosemary essential oil and its constituent monoterpenes, such as borneol, have been found to inhibit bone resorption in the rat (Muhlbauer et al 2003). Aqueous and ethanol extracts of rosemary have been found to produce significant antinociceptive activity and diminish morphine withdrawal syndrome in rats (Hosseinzadeh & Nourbakhsh 2003).

Rosemary extract may delay and inhibit tumour formation in women with breast cancer (Abascal & Yarnell 2001) and prevent mesangial cell proliferation in cultured murine mesangial cells (Makino et al 2000).

When used topically, rosemary essential oil is said to stimulate the skin and increase blood circulation (Blumenthal et al 2000).

CLINICAL USE

Increased mental concentration

One of the main traditional uses of rosemary oil is to increase mental concentration and memory. This is supported by a RCT of 140 subjects that found that rosemary produced a significant enhancement

of performance for overall quality of memory and secondary memory factors, with an impairment of speed of memory compared with controls (Moss et al 2003). Further support comes from an observational study in 40 adults where 3 minutes' exposure to rosemary essential oil was seen to decrease frontal alpha and beta power, suggesting increased alertness. Subjects felt more relaxed and alert, had lower anxiety scores and were faster, but not more accurate, at completing maths computations (Diego et al 1998). A small, case series of 10 subjects also found that rosemary essential oil had positive effects on mood concentration and memory (Svoboda et al 2002). Moss et al 2003 demonstrated significantly enhanced overall memory quality but impaired memory speed using rosemary essential oil placed on diffuser pads in an aroma stream placed in test cubicles and switched on for 5 min prior to testing (n = 140, divided into three groups: lavender, rosemary and control).

Alopecia

The traditional use of rosemary to stimulate hair growth is supported by a 7-month, randomised, double-blind study of 86 patients that found rubbing oils (thyme, rosemary, lavender and cedarwood) into the scalp helped with alopecia for 44% of patients versus 15% of controls (Hay et al 1998). Although promising, the role of rosemary as a standalone substance in achieving these results is unclear.

Antispasmodic

Rosemary is widely acknowledged to be a carminative and is used internally as an antispasmodic for mild cramp-like gastrointestinal and biliary upsets, as well as for tension headache, renal colic and dysmenorrhoea (Blumenthal et al 2000). It is also used to relax bronchial smooth muscle in the treatment of asthma (al-Sereiti et al 1999), but controlled studies are unavailable to determine clinical efficacy.

Chemoprotective and adjunct in cancer therapy

Rosemary was used topically to treat cancer in ancient Greece and South America. Although controlled trials are yet to be conducted, it has been suggested that rosemary may delay and inhibit tumour formation in women with breast cancer (Abascal & Yarnell 2001) and that it has potential as a preventive agent or as an adjunct in cancer therapy. An in vitro study in human breast cancer cells found that rosemary extract increased the intracellular accumulation of commonly used chemotherapeutic agents, including doxorubicin and vinblastine via inhibition of P-glycoprotein, thereby overcoming multidrug resistance in tumour cells (Plouzek et al 1999). Clinical studies are required to determine whether the effect is significant.

OTHER USES

When applied topically, rosemary oil may stimulate the blood supply and act as supportive therapy for rheumatic conditions and circulatory problems (Blumenthal et al 2000). Topically, rosemary has also been used for wound healing, as an insect repellent and to treat toothache and eczema. Rosemary extract cream preparations have been shown to protect against sodium lauryl sulfate-induced irritant contact dermatitis (Fuchs et al 2005).

In a small, uncontrolled, prospective pilot study of eight women, rosemary in combination with 11 other botanical extracts was found to relieve menopausal symptoms (Smolinski et al 2005).

DOSAGE RANGE

- Infusion of dried leaf: 2–4 g three times daily.
- Fluid extract (45%): 1–4 mL three times daily.
- Topical preparations containing 6–10% essential oil can be applied directly to skin. Often a carrier oil, such as almond oil, is used as a vehicle for the essential oil.
- Bath additive: 10 drops essential oil added to bath.

ADVERSE REACTIONS

Rosemary is generally recognised as safe for human consumption in quantities used as food. Consuming large amounts of rosemary may cause stomach and intestinal irritation, as well as seizures, owing to the high content of highly reactive monoterpene ketones, such as camphor (Burkhard et al 1999). Topically, rosemary is not considered to be highly allergenic; however, allergic contact dermatitis from rosemary has been reported (Fernandez et al 1997, Hjorther et al 1997, Inui & Katayama 2005), as has asthma from repeated occupational exposure (Lemiere et al 1996). Rosemary essential oil should be diluted before topical application to minimise irritation.

SIGNIFICANT INTERACTIONS

Controlled studies are not available; therefore, interactions are based on evidence of activity and are largely theoretical and speculative.

Iron

Rosemary extracts are widely used as an antioxidant to preserve foods; however, the phenolic-rich extracts may reduce the uptake of dietary iron (Samman et al 2001). Separate doses by 2 h.

Anticoagulants

Increased bruising and bleeding theoretically possible — use caution.

Drugs dependent on P-glycoprotein transport

Theoretically, increased drug uptake can occur with those drugs dependent on P-glycoprotein transport. The clinical significance of this finding remains to be tested, although it has been suggested that this activity may be used to enhance the effects of chemotherapeutic agents (Plouzek et al 1999).

CONTRAINDICATIONS AND PRECAUTIONS

None known.

PREGNANCY USE

Rosemary has been shown to have an anti-implantation effect in rats, without interfering with normal fetal development postimplantation (Lemonica et al 1996). It is not recommended in pregnancy in doses higher than the usual dietary intake levels until safety is established or only under professional supervision.

PRACTICE POINTS/PATIENT COUNSELLING

- Rosemary is widely used as a food seasoning and preservative.
- Rosemary extract exhibits antioxidant, antibacterial, anti-inflammatory, hepatoprotective and chemoprotective activities in various in vitro and experimental models.
- Rosemary oil is widely used to assist in concentration and memory and to stimulate blood flow.
- Traditionally, it has been used to relieve stomach, gall bladder and menstrual cramps, but its internal use has not yet been significantly investigated in controlled studies.
- Rosemary is generally safe when the leaves are consumed in dietary amounts, although excessive intake may cause stomach irritation and seizures in susceptible people.

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S-Adenosyl-L-methionine (SAMe)

HISTORICAL NOTE SAMe was first discovered in Italy in 1952. About 20 years later, a stable salt was commercially manufactured and produced for injectable use. At first, it was investigated as a treatment for schizophrenia, for which it proved inappropriate; however, successful trials in depressed patients began in the 1970s and it was inadvertently found to improve symptoms of arthritis. Since then, numerous studies have been undertaken to examine the role of SAMe in treating depression, osteoarthritis and liver pathology. To date, more than 75 clinical trials have been conducted using SAMe as a therapeutic agent, involving over 23,000 people.

BACKGROUND AND RELEVANT PHARMACOKINETICS

SAMe is synthesised in the cytosol of every cell, with the liver being the major site of biosynthesis and degradation. Up to half the daily methionine is converted to SAMe in the liver, where it is metabolised to *S*-adenosylhomocysteine and then homocysteine (Hcy). Being a central part of the one-carbon metabolism cycle, SAMe is intrinsically linked with the other methyl donors such as folate and B12.

SAMe naturally exists as diastereoisomers and it is presently unclear whether both the R and S forms are biologically active in humans. Evidence from a rat model suggests that they are equipotent (Dunne et al 1998). Oral doses achieve peak plasma concentrations within 3–5 h after ingestion of an enteric-coated tablet (400–1000 mg). Enteric coating of SAMe supplements is essential to ensure product stability and potency. The half-life is reported to be 100 min, and excretion occurs via both urine and faeces (Najm et al 2004).

MAIN ACTIONS

SAMe is involved in myriad biochemical processes and metabolic pathways, chiefly as a methyl donor. It is involved in the synthesis of many important biochemicals, such as creatine, melatonin, glutathione, RNA and DNA, phospholipids, proteins, adrenaline and amino acids L-cysteine and taurine. SAMe is closely linked with the metabolism of folate and vitamin B12.

This review only discusses those actions that have been confirmed clinically.

Antidepressant activity

SAMe supplementation produces a clinically significant antidepressant activity that has been demonstrated in numerous trials.

The mode of antidepressant action is unknown, but is likely to involve several mechanisms. As a methyl donor, SAMe plays a role in the metabolism of various CNS neurotransmitters that play an integral part in synaptic transmission and behaviour, such as noradrenaline, dopamine and serotonin (Bottiglieri 1996). Supplementation with SAMe in depressed patients raises serotonin, dopamine and phosphatidylserine and improves neurotransmitter binding to receptor sites, resulting in increased activity (Pizzorno & Murray 2006). More recent evidence suggests that the dopaminergic activity is most prominent. One human study confirmed that 7 days of supplemental SAMe

(400 mg/day) decreased the exaggerated plasma noradrenaline levels found in depressed patients (Sherer et al 1986). It is also involved in the formation of phosphatidylcholine, a major component of cell membranes and neurotransmission (Carney et al 1987).

Interestingly, significantly low levels of SAMe in cerebrospinal fluid have been observed in severely depressed patients compared with controls (Bottiglieri et al 1990); however, the significance of this finding is unknown.

Anti-inflammatory

A substantial body of evidence has identified clinically significant anti-inflammatory activity for SAMe with comparative trials showing it to be as effective as standard NSAIDs.

Although the mechanism of action remains unclear, it does not appear to be mediated by PG. SAMe stimulates the synthesis of proteoglycans by articular chondrocytes and exerts a chondroprotective effect, according to in vitro research and tests with experimental animals (Barcelo et al 1987, Clayton 2007, Harmand et al 1987). In vitro studies using cultured rabbit synovial cells has found that SAMe reduces TNF-alpha and fibronectin RNA expression (Gutierrez et al 1997). Clinical responses suggest a concomitant analgesic property; however, once again, the mechanism for this remains unknown (Clayton 2007).

Hepatoprotective effects

SAMe indirectly reduces oxidative stress in the liver by serving as a precursor for glutathione. Glutathione is particularly important for reducing the toxic effects of free radical molecules generated by various substances, including alcohol. SAMe also acts as the main methylating agent in the liver. Research with people with alcoholic and non-alcoholic liver diseases confirms that SAMe supplementation significantly increases hepatic glutathione levels (Vendemiale et al 1989). Additionally, in vitro research has identified antifibrotic activity and, recently, enhanced production of IL-6, a key anti-inflammatory cytokine in the liver that assists regeneration and downregulation of TNF (Arteel et al 2003, Casini et al 1989, Song et al 2004). Research using animal models demonstrates that SAMe is a natural growth regulator in hepatocytes and is anti-apoptotic in healthy liver cells, but pro-apoptotic in hepatic carcinoma cells (Lu & Mato 2005).

OTHER ACTIONS

Prolactin and thyroid stimulating hormone (TSH) effects

A double-blind, placebo-controlled study involving 20 subjects with depression identified a significant reduction in prolactin concentrations following 14 days of SAMe treatment (Thomas et al 1987). The results of a study conducted in 1990, however, suggest that the effects on these hormones may be gender specific, with women demonstrating an augmenting response of TSH and no effect on prolactin levels, whereas release of both TSH and prolactin was inhibited in male subjects (Fava et al 1990). If SAMe does exert dopaminergic effects, as presently suspected, then it should also be taken into consideration that dopamine naturally inhibits both TSH and prolactin secretion in humans.

Antioxidant

SAMe exhibited direct antioxidant activity in vitro (Caro & Cederbaum 2004).

CLINICAL USE

Although SAMe is administered as an oral supplement in Australia, it is also used in injectable dose forms in Europe. This discussion will mainly focus on oral use.

Osteoarthritis (OA)

A 2004 meta-analysis of 11 RCTs involving almost 1500 patients, comparing SAMe with either placebo or NSAIDs, concluded that SAMe is as effective as NSAIDs in reducing pain and improving functional limitation in patients with OA of the knee. In addition, SAMe-treated patients were 58% less likely to experience adverse effects than those treated with NSAIDs (Soeken et al 2002).

The longest clinical trial to date was conducted over 2 years and found that a loading dose of oral SAMe 600 mg/day taken over the first 2 weeks, followed by a maintenance dose of 400 mg, produced an improvement in symptoms within the first month and no serious adverse effects (Konig 1987).

Comparative studies

Comparative studies in humans have found that oral SAMe (1200 mg) produces similar symptom-relieving effects as piroxicam (20 mg), ibuprofen (1200 mg), indomethacin (150 mg) or naproxen (750 mg) (Caruso & Pietrogrande 1987, Glorioso et al 1985, Maccagno et al 1987, Muller-Fassbender 1987, Vetter 1987).

A 16-week randomised, double-blind, crossover study of 61 individuals with OA of the knee compared the efficacy of SAMe (1200 mg/day) with celecoxib (200 mg/day). At this dose, SAMe was as effective as celecoxib in providing significant symptom relief; however, it had a slower onset of action, requiring 1 month of continuous use before benefits were felt (Najm et al 2004). It has been suggested that the antidepressant activity may be a confounding factor in these trials; however, another trial (Clayton 2007) was unable to detect an antidepressant effect for SAMe.

Depression

Several reviews and at least two meta-analyses have examined the available evidence for SAMe for trials completed prior to 1994 and have concluded that SAMe is superior to placebo, is as effective as standard tricyclic antidepressants and is better tolerated in the treatment of depressive disorders (Bressa 1994, Fetrow & Avila 2001).

The review conducted in 2005 assessed results from 11 studies and concluded that the evidence for SAMe was positive in depression, but currently hampered by the short duration of trials and

questions over the oral bioavailability of the products used (Williams et al 2005). Advantages consistently noted by reviewers include the faster onset of action observed with SAMe-treated patients (10 days) compared to treatment with SSRIs (21 days) and the lack of many side effects that plague the pharmaceutical antidepressants (Mischoulon & Fava 2002).

A trial implementing 800–1600 mg/day SAMe as an adjunctive agent in 30 treatment-resistant patients over a 6-week trial revealed a staggering 50% response rate, with 43% of the sample experiencing remission of symptoms (Alpert et al 2004). Positive results such as these warrant further investigation of SAMe in this adjunctive role with more stringent trial designs. Due to case reports of agitation and mania in bipolar patients taking this nutraceutical, SAMe should not be used in the depressive phase of this condition, until more research is conducted (Andreescu et al 2008, Bogarapu et al 2008).

Parkinson's disease and depression

High-dose SAMe (800–3600 mg/day) treatment was investigated in a pilot study involving 11 depressed patients with Parkinson's disease, all of whom had been previously treated with other antidepressant agents and had no significant benefit or intolerable side effects. After 10 weeks, 10 patients had at least a 50% improvement on the Hamilton Depression Scale, with only one patient showing no improvement. The mean score before treatment was 27.09 and was 9.55 after SAMe treatment (Di Rocco et al 2000).

Fibromyalgia

Four double-blind trials have investigated the effects of SAMe in fibromyalgia, with all reporting positive findings (Jacobsen et al 1991, Tavoni et al 1987, 1998, Volkmann et al 1997) such as reduced number of trigger points and areas of pain, improved mood and reduced fatigue (Sarac & Gur 2006). Two studies used injectable SAMe (200 mg daily).

The largest study involved 44 patients with primary fibromyalgia and found that during week 5, the group receiving SAMe (800 mg/day) experienced improvements in clinical disease activity, pain, fatigue, morning stiffness and one measurement of mood. Although encouraging, not all parameters were improved beyond placebo, such as tender point score and isokinetic muscle strength (Jacobsen et al 1991).

These results should not be surprising, given that one-third of all fibromyalgia patients are reported to suffer from depression and a meta-analysis of the effectiveness of antidepressants (including SAMe) in fibromyalgia deemed them a successful treatment strategy (O'Malley et al 2000). It concluded that tricyclic antidepressants, SSRIs and SAMe all improved sleep, fatigue, pain and wellbeing, but not necessarily trigger points.

Schizophrenia

Eighteen patients with chronic schizophrenia were randomly assigned to receive either SAMe (800 mg) or placebo for 8 weeks in a double-blind study. Active treatment resulted in some reduction in aggressive behaviour and in improved quality of life. This is a notable finding, as improvement in quality of life is considered a critical outcome measure in the management of schizophrenic illness. Interestingly, female patients also showed improvement of depressive symptoms and clinical improvement did not correlate with serum SAMe levels. Two patients in the active group exhibited some exacerbation of irritability; however, it is unclear whether the effect was due to SAMe administration or whether it was an unrelated deterioration, as relapse is common in patients with chronic schizophrenia. Further studies using larger samples are required to test these initial findings.

Liver cirrhosis

It is now generally accepted that in alcoholic patients with advanced liver cirrhosis, hepatic SAMe concentration is greatly decreased through alcohol exposure (Cave et al 2007, Kharbanda 2007, Lieber 2002). While transient SAMe depletion is necessary for the liver to regenerate, chronic hepatic SAMe depletion may lead to malignant transformation (Lu & Mato 2005, 2008). In the interim-depressed hepatic SAMe, especially together with a reduced SAM:SAH (S-adeonsylhomocysteine) ratio, results in impaired transmethylation, producing increased fat deposition, apoptosis and accumulation of damaged proteins — all characteristic features of liver injury (Cave et al 2007, Kharbanda 2007). Primate studies have found that decreased hepatic SAMe concentrations and associated liver lesions, including mitochondrial injury, can be corrected with SAMe supplementation (Lieber et al 1990), with reduced markers of lipid peroxidation, histological evidence of liver injury and maintained mitochondrial glutathione (GSH) (Cave et al 2007).

A 2006 Cochrane review of SAMe in alcoholic liver disease analysed results from nine randomised clinical trials that included a heterogeneous sample of 434 patients (Rambaldi & Gluud 2006). The methodological quality was considered low; however, eight of the trials were placebo controlled. As a result, the analysis was based mainly on one trial that found no significant effects of SAMe on all-cause mortality, liver-related mortality, liver transplantation or complications. The authors concluded that based on such limited evidence, more long-term, high-quality randomised trials of SAMe for these patients are required before SAMe may be recommended for clinical practice.

Non-alcoholic fatty liver disease (NAFLD) or non-alcoholic steatohepatitis (NASH)

Human studies have demonstrated that patients with liver disease have an impaired ability to convert methionine to SAMe and decreased plasma and hepatic GSH levels (Cave et al 2007. SAMe has been shown to improve GSH in patients with liver disease after 6 months of oral therapy. Of particular interest is recent evidence from animal studies which suggest that SAMe depletion in the early stages of NASH may be a key point of disease progression into NAFLD (Lu & Mato

2008, Wortham et al 2008). Clinical trials have demonstrated benefit from SAMe therapy in various forms of liver disease, including alcoholic cirrhosis and intrahepatic cholestasis of pregnancy. SAMe supplementation has also demonstrated attenuation of inflammation and liver injury in a nutritional deficiency model of steatohepatitis and clinical trials in NASH patients are currently under way (Cave et al 2007). In lieu of more solid evidence to support SAMe as a therapeutic agent in NASH and NAFLD, the preferred current treatment is betaine, which by virtue corrects SAMe depletion (Kharbanda 2007, Kwon et al 2008).

Hepatic cancer

Due to its role in the regulation of growth and apoptosis of hepatocytes, SAMe is being investigated as a possible preventative or treatment agent in hepatocellular carcinoma (Lu & Mato 2005, 2008).

OTHER USES

SAMe is used to reduce pain in migraine headache because analgesic activity was reported at a dose of 400–800 mg/day in a group of migraine sufferers (Gatto et al 1986). It is also used in AIDS-related myelopathy and coronary artery disease, as these conditions have been associated with depleted SAMe levels. Supplementation has also been prescribed in cases of general fatigue, poor digestion, allergies and elevated homocysteine levels.

DOSAGE RANGE

Based on clinical studies

- Depression: 400–1600 mg/day in divided doses. Usually 1200–1600 mg/day. Sometimes it is started as 200 mg twice daily, increased on day 2 to 400 mg twice daily and then increased again to 400 mg three times daily on day 10, until reaching the full therapeutic dose of 400 mg four times daily by day 20, if necessary (Pizzorno & Murray 2006).
- Osteoarthritis: 1200 mg/day in divided doses, taken as above, with a reduced dose of 400 mg/day used as a maintenance dose once a response occurs.
- Fibromyalgia: 600–800 mg/day in divided doses.
- Liver diseases: 400–1200 mg/day in divided doses, although larger doses have been used.
- Parkinson's disease: 800–3600 mg/day in divided doses.
- Migraine: 400–800 mg/day in divided doses.
  - Reducing aggression in schizophrenia: 800 mg/day (only under supervision).

ADVERSE REACTIONS

Orally, SAMe is generally well tolerated. Mild gastrointestinal discomfort is the most common side effect reported in clinical studies, although anxiety, headache, urinary frequency, dizziness, nervousness, sweating and pruritis have also been reported. It has been reported that side effects are more likely with higher doses and may be minimised by consuming SAMe before food.

SIGNIFICANT INTERACTIONS

Controlled studies are not available; therefore, interactions are based on evidence of activity and are largely theoretical and speculative.

Tricyclic antidepressants and other serotonergic agents

Theoretically, co-administration may result in an increased risk of serotonin syndrome. However, one experimental study found that brain SAMe levels were significantly reduced after chronic treatment with imipramine (Taylor & Randall 1975) — use this combination with caution.

Hepatotoxic drugs

SAMe may reduce hepatic injury caused by such agents as paracetamol, alcohol and oestrogens — potentially beneficial interaction.

L-Dopa

SAMe methylates levodopa, which could theoretically reduce the effectiveness of levodopa given for Parkinson's disease; however, the effect has not been observed clinically — observe patients.

Thyroxine

Caution and monitoring may be warranted.

Betaine

In studies supplementing mice with betaine, significant increases in SAMe were observed with a three-fold elevation of the activity of methionine adenosyltransferase — observe.

CONTRAINDICATIONS AND PRECAUTIONS

SAMe should be avoided in people with bipolar disorder and used with caution by people with schizophrenia or schizoaffective disorder, or Parkinson's disease (Guidotti 2007, Pizzorno & Murray 2006).

PREGNANCY USE

SAMe has been used intravenously in the last trimester of pregnancy with no adverse effects to mother or fetus. However, safety has not yet been conclusively established for either injectable or oral dose forms and possible effects on prolactin levels need to be considered.

PATIENTS' FAQs

What will this supplement do for me?

SAMe has anti-inflammatory, analgesic, antidepressant and protective effects on the liver. It effectively reduces pain and inflammation in OA and elevates mood in depression. In fibromyalgia, SAMe reduces pain, fatigue and morning stiffness and may also reduce pain in migraine headache.

When will it start to work?

Beneficial effects are usually seen within 4–5 weeks for OA, whereas antidepressant effects are experienced within 1 week. Benefits in fibromyalgia can take up to 6 weeks to establish.

Are there any safety issues?

SAMe should be used with caution by people with bipolar disorder, schizophrenia or schizoaffective

disorder, Parkinson's disease or taking antidepressant medicines. Monitoring of homocysteine levels may be required with long-term supplementation.

PRACTICE POINTS/PATIENT COUNSELLING

- SAMe is involved in myriad biochemical reactions within the body and found within every cell.
- Clinically, it has anti-inflammatory, analgesic, antidepressant and hepatoprotective activities.
- A 2002 meta-analysis concluded that SAMe is as effective as NSAIDs in reducing pain and improving functional limitation in patients with OA without the adverse effects associated with NSAIDs. A recent study has found that it is as effective as celecoxib for providing symptom relief; however, SAMe has a slower onset of action.
- Clinical trials have also shown it to be a safe and effective treatment for depression, comparable with tricyclic antidepressant drugs, yet with a faster onset of action.
- SAMe also appears to be useful in fibromyalgia, and possibly migraine headache. Its usefulness in alcoholic liver disease is unclear. Other uses include treatment of general fatigue, elevated homocysteine levels, allergies and poor digestion.

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Sage

HISTORICAL NOTE The *Salvia* genus is one of the largest groups of the Lamiaceae family with over 700 species spread throughout the world (Nickavar et al 2005). Sage has been used since ancient times as an antiseptic, astringent, tonic, carminative, antispasmodic, anti-inflammatory and to reduce sweating agent in various traditional medicine systems. The name 'Salvia' derives from the Latin salvere (to be saved) (Blumenthal et al 2000). Sage oil is used as a culinary spice and as a fragrance in soaps and perfumes. The fragrance is said to suppress the odour of fish.

OTHER NAMES

Broad-leafed sage, common sage, dalmatian sage, garden sage, meadow sage, Spanish sage, true sage

BOTANICAL NAME/FAMILY

Salvia officinalis, *Salvia lavandulaefolia*, *Salvia hypoleuca* Benth (family Labiatae or Lamiaceae).

PLANT PART USED

Leaf

CHEMICAL COMPONENTS

The exact chemical constituents depend on geographic and climatic conditions as well as harvesting conditions, distillation method and the part of the plant used (Nickavar et al 2005). The leaves contain up to 2.5% essential oil, which contains thujone, cineol and camphor, as well as humulene, pinene, camphene, limonene, carnosol and rosmarinic acid. In addition, the leaves contain catechin-type tannins, diterpene bitter principles, triterpenes, steroids, flavones, and flavonoid glycosides, together with polysaccharides. Sage is a rich source of beta-carotene, vitamins C and B-complex (Fisher & Painter 1996). The flowering parts of *S. hypoleuca* contain bicyclogermacrene, (E)-beta-caryophyllene, viridifloral, spathulenol, beta-pinene and delta-pinene. Pharmacopoeial grade sage leaf must contain not less than 1.5% thujone-rich volatile oil (Blumenthal et al 2000).

MAIN ACTIONS

Antimicrobial

Sage is reported to have antimicrobial activity attributed to the thujone, thymol and eugenol contents of the volatile oil (Shapiro et al 1994), as well as its rosmarinic acid content (Petersen & Simmonds 2003). The phenolic acids, salvins and monomethyl ethers have also been attributed with antimicrobial activity. Overall, activity has been reported in vitro against *Staphylococcus aureus*, *Escherichia coli*, *Salmonella* spp, *Shigella sonnei*, *Klebsiella ozanae*, *Bacillus subtilis* and various fungi, including *Candida albicans* (Newell et al 1996). Phenolic extracts have also shown antibacterial activity against *Enterococcus* (Feres et al 2005). Sage had some in vitro antimicrobial effects on saliva samples from periodontally healthy and diseased subjects, although it had less activity than clove or propolis (Feres et al 2005). Sage essential oil has been shown to have effective inhibitory activity against microorganisms, such as *Klebsiella* spp, *Enterobacter* spp, *E. coli*, *Proteus mirabilis* and *Morganella morganii*, isolated from urinary tract infection (Santos Pereira et al 2004). There are also reports that sage may also be fungistatic and virustatic (Eidi et al 2005).

Antioxidant

Sage extracts have been shown to have strong antioxidant activity (Matsingou et al 2003, Pizzale et al 2002), with labiatic acid and carnosic acid reported to be the active compounds (Perry et al 2003). According to in vivo studies with animal models, ingestion of sage infusion improves the liver's antioxidant status (Lima et al 2005) and protects against azathioprine-induced toxicity (Amin & Hamza 2005). However, sage essential oil did not show protective effects against toxicity from an oxidative compound in isolated rat hepatocytes (Lima et al 2004).

Astringent

The high tannin content of sage supports its reported astringent activity.

Antispasmodic
Sage oil has antispasmodic effects in laboratory animals (Newell et al 1996) and this is likely due to the irritating effects of the volatile oil. There is some evidence that sage oil may also exert a centrally mediated antisecretory action.

Anxiolytic
Rosmarinic acid, which is a component of sage essential oil, produces an anxiolytic-like effect without exerting locomotor alterations or DNA damage in the brain tissue of rats (Pereira et al 2005). According to in vitro tests, compounds in the methanolic extract have an affinity for human brain benzodiazepine receptors (Kavvadias et al 2003).

Anticholinesterase
In vitro and in vivo studies suggest that sage essential oil and some individual monoterpenoid constituents inhibit acetylcholinesterase activity (Perry et al 2003). An extract of the sage leaf exhibited dose-dependent, in vitro inhibition of acetylcholinesterase (Kennedy & Scholey 2006).

OTHER ACTIONS
The water-soluble polysaccharide complex from sage has demonstrated immunomodulatory activity (Capek & Hribalova 2004) and the terpenoid fractions have shown antimutagenic properties in vivo (Vujosevic & Blagojevic 2004). In vitro and in vivo studies indicate that sage essential oil and some individual monoterpenoid constituents demonstrate antioxidant, anti-inflammatory and oestrogenic effects (Perry et al 2003).

Sage extract has been found to also significantly decrease serum glucose in diabetic rats without affecting insulin release, suggesting a possible role in diabetes (Eidi et al 2005). It has been suggested that extracts of sage containing carnosic acid may act as a new class of lipid absorption inhibitor. A methanolic extract of sage has also shown significant inhibitory effect on serum triglyceride elevation in olive oil-loaded mice, and inhibitory activity against pancreatic lipase, mainly because of the carnosic acid content. Carnosic acid was also found to reduce the weight gain and accumulation of epididymal fat in high-fat diet-fed mice after 14 days (Ninomiya et al 2004).

CLINICAL USE
Although sage has not been the subject of many clinical studies, many of its constituents demonstrate significant pharmacological effects, providing a theoretical basis for some of its uses.

Reduces secretions
Sage has been traditionally used to treat excessive perspiration and salivation, dysmenorrhoea, diarrhoea, galactorrhoea and sweats associated with menopause and to cease lactation (Fisher & Painter 1996). An open study of 80 patients confirmed that it can reduce perspiration (Blumenthal et al 2000). The high tannin content of the herb provides a theoretical basis for its use.

Dyspepsia and lack of appetite
Sage's reported antispasmodic action and bitter constituents support its use in treating loss of appetite, gastritis, flatulence, bloating and dyspepsia. These uses await support from clinical research.

Inflammation of mucous membranes
Topically, sage is used as a gargle for laryngitis, pharyngitis, stomatitis, gingivitis, glossitis, minor oral injuries and inflammation of the nasal mucosa (Blumenthal et al 2000). These uses can be based on the pharmacological activity of its chemical components. In an open-label, single-blind RCT of 420 patients, the non-steroidal anti-inflammatory drug benzydamine hydrochloride was found to be more effective than sage in relieving postoperative pain when used as a mouthwash after tonsillectomy in children and adults (Lalicevic & Djordjevic 2004).

Sage has been found to have less antitussive effects than codeine, but a significantly higher or similar effect to dropropizine (Nosalova et al 2005). A small double-blind study has suggested that use of an essential oil spray or gargle formulation that includes sage may help relieve snoring (Prichard 2004).

Pharyngitis
A randomised, double-blind, parallel group study compared the efficacy and tolerability of spray (containing a *Salvia officinalis* fluid extract) against placebo in the treatment of patients with acute viral pharyngitis (Hubbert et al 2006). A total of 286 patients with subjective and objective evidences of pharyngitis were randomised to receive placebo or treatment for 3 days, including one baseline visit and one final visit. The 15% spray containing 140 microlitre sage extract per dose was statistically significantly superior to placebo in reducing the throat pain intensity score. Symptomatic relief occurred within the first 2 h after first administration and only minor side effects such as dry pharynx or burning of mild intensity were seen.

Memory enhancement
Since ancient times, sage has been used to enhance memory and treat dementia. More recently, cholinergic activities have been demonstrated in vitro and in vivo, suggesting that it may be useful in treating Alzheimer's disease (Perry et al 2001). A randomised placebo-controlled study undertaken at three centres assessed the effects of sage extract (60 drops/day) in 42 subjects with mild-to-moderate Alzheimer's disease (Akhondzadeh et al 2003). Initially, subjects had a score of 12 or less on the cognitive subscale of Alzheimer's Disease Assessment Scale (ADAS-cog) and two or less on the Clinical Dementia Rating (CDR). At 4 months, sage extract produced a significantly better outcome on cognitive functions than placebo in both test scales and was well tolerated.

In 2003, two placebo-controlled, double-blind, crossover studies involving 44 healthy young adults investigated the effects of different strengths of standardised essential oil of *S. lavandulaefolia* on memory (Tildesley et al 2003). Both studies found

that a 50-microlitre dose of *Salvia* essential oil significantly improved immediate word recall and was able to modulate cognition. In another placebo-controlled, double-blind, crossover study involving 24 subjects, Spanish sage (*S. lavandulaefolia*) essential oil was found to enhance cognitive performance and mood in healthy young adults (Tildesley et al 2005).

In 2006, results of a double-blind, placebo-controlled, crossover study were published involving 30 healthy participants who received a series of different treatments on each visit to the research laboratory (placebo, 300, 600 mg dried sage leaf) (Kennedy & Scholey 2006). The results confirm previous observations of the cholinesterase inhibiting properties of *S. officinalis*, and improved mood and cognitive performance following the administration of single doses to healthy young participants.

Menopausal symptoms

Sage is commonly used by modern herbalists in prescriptions for menopause in order to treat hot flushes, night sweats, and for its oestrogenic effect. As yet, there is no clinical evidence available to confirm effectiveness for these indications (Blumenthal et al 2000).

OTHER USES

As an inhalant, sage is used for asthma. In foods, it is used as a culinary spice. In manufacturing, sage is used as a fragrance component in soaps and cosmetics. Topically, sage is used to treat herpes labialis, laryngitis, pharyngitis, stomatitis, gingivitis, glossitis, minor oral injuries and inflammation of the nasal mucosa.

DOSAGE RANGE

Internal use

- Infusion of dried herb: 1–4 g three times daily.
- Tincture (1:1): 1–4 mL three times daily.
- Essential oil: 2–3 drops in 100 mL water several times daily.
- Gargle or rinse (use warm infusion): 2.5 g cut leaf in 100 mL water; or 2–3 drops essential oil in 100 mL water; or use 5 mL fluid extract diluted in a glass of water, several times daily.

TOXICITY

Sage is likely to be safe when taken in amounts typically found in foods, although sage oil contains thujone, which may be toxic in large doses. In large amounts, the camphor and thujone content of sage oil have been shown to have convulsant properties in rats (Millet et al 1981) and when taken internally in large amounts, sage may cause restlessness and seizures in humans (Blumenthal et al 2000, Newell et al 1996). Sage tea has also been reported to cause cheilitis and stomatitis, dry mouth and local irritation.

ADVERSE REACTIONS

One double-blind, randomised trial found that it was well tolerated and produced fewer side effects than placebo (Akhondzadeh et al 2003). Occasional allergic reactions with topical use have been reported.

SIGNIFICANT INTERACTIONS

Iron, calcium, magnesium

Due to the tannin content, sage may reduce the absorption of these minerals — separate doses by 2–3 hours.

CONTRAINDICATIONS AND PRECAUTIONS

Sage oil can irritate the skin when used topically. Internal use of the essential oil should be closely monitored.

PREGNANCY USE

Traditionally, sage is reported to have abortifacient properties. Its use in pregnancy is therefore not recommended (Mills & Bone 2000, Newell et al 1996).

PRACTICE POINTS/PATIENT COUNSELLING

- Sage is a widely used, popular spice and sage oil is used in a variety of culinary applications.
- Sage has a long history of use in traditional medicine as an antispasmodic and carminative, to relieve excess sweating and as a gargle for inflammations of the mouth.
- It is also commonly prescribed in combination with other herbs to relieve menopausal symptoms such as night sweats.
- Sage contains volatile oils and tannins that are thought to be the key constituents responsible for most of its pharmacological actions.
- It also has antibacterial and some antifungal activities.
- A recent double-blind study suggests it may be useful in mild-to-moderate Alzheimer's disease. Other studies report that it improves memory in healthy subjects.
- Sage is likely to be safe when taken in amounts typically found in foods.

PATIENTS' FAQs

What will this herb do for me?

Sage is used to reduce symptoms of menopause such as night sweats; however, scientific testing has not been conducted to confirm whether it is effective. Recent research suggests that it may improve memory in Alzheimer's disease and in healthy subjects.

When will it start to work?

The study in Alzheimer's disease found effects established within 4 months' use. In the case of menopause, a time frame is unknown.

Are there any safety issues?

When used in appropriate doses, it appears to be a safe herbal medicine; however, it should not be used in pregnancy.

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St John's wort

HISTORICAL NOTE St John's wort (SJW) has been used medicinally since ancient Greek times when, it is believed, Dioscorides and Hippocrates used it to rid the body of evil spirits. Since the time of the Swiss physician Paracelsus (c. 1493–1541), it has been used to treat neuralgia, anxiety, neurosis and depression. Externally, it has also been used to treat wounds, bruises and shingles. The name 'St John's wort' is related to its yellow flowers, traditionally gathered for the feast of St John the Baptist and the term 'wort' is the old English word for plant. SJW has enjoyed its greatest popularity in Europe and comprises 25% of all antidepressant prescriptions in Germany (Schrader 2000). In the past few decades, its popularity has grown in countries such as Australia and the United States.

OTHER NAMES

Amber, balsana, devil's scourge, goatweed, hardhay, hartheu, herb de millepertuis, hierba de San Juan, hypericum, iperico, johanniskraut, klamath weed, konradskraut, millepertuis, rosin rose, sonnenwendkraut, St Jan's kraut, tipton weed, witch's herb

BOTANICAL NAME/FAMILY

Hypericum perforatum (family Clusiaceae or Guttiferae)

PLANT PARTS USED

Aerial parts, flowering tops

CHEMICAL COMPONENTS

Naphthodianthrones (including hypericin and pseudohypericin). Flavonoids, mostly hyperoside, rutin, quercetrin, isoquercitrin, quercetin and kaemferol, phenolics, including hyperforin, procyanidins, essential oil, sterols (beta-sitosterol), vitamins C and A, xanthones and choline.

Manufactured products will vary in the concentrations and proportions of the different plant constituents present because these are influenced by the plant's place of origin, its harvest time and drying, extraction processes and storage conditions. Hyperforin, in particular, can be present in variable concentrations because it is unstable in light, air and most organic solvents (Mennini & Gobbi 2004). This is extremely important to remember when comparing studies, as variations in chemical composition could be responsible for differences in results. It also provides a rationale for lack of interchangeability between brands.

MAIN ACTIONS

Due to the combined effect of several active constituent groups, SJW has many pharmacological actions.

Antidepressant

Although SJW has been investigated extensively in scientific studies, there are still many questions about its pharmacology and mechanisms of action.

Collectively, the data show that SJW extract exerts significant pharmacological activity within several neurochemical systems believed to be implicated in the pathophysiology of depression.

Inhibits synaptic reuptake of several neurotransmitters

Preclinical animal studies have found that SJW inhibits the synaptic reuptake system for serotonin, noradrenaline and dopamine (Nathan 1999, Wonnemann et al 2001). Studies using specific isolated constituents have demonstrated potent uptake inhibition of gamma aminobutyric acid (GABA) and L-glutamate in vivo (Bilia et al 2002, Chatterjee et al 1998). These effects appear to be non-competitive, dose-dependent and mediated via sodium channels (Roz & Rehavi 2004). Studies with hyperforin have shown that it acts by reducing the pH gradient across the synaptic vesicle membrane, resulting in diffusion of uncharged monoamines out of the vesicular compartment into the cytoplasm. The increase in cytoplasmic concentration in turn decreases the transmembrane gradient of the neurotransmitters causing an 'apparent' inhibition of synaptosomal uptake by hyperforin. This is a novel mechanism of action, which differs from conventional antidepressant drugs.

Although hyperforin is the main constituent responsible for these effects, tests now show that a number of others are also involved (Gobbi et al 2001), such as adhyperforin, which has demonstrated a strong inhibitory effect on neurotransmitter uptake, and the oligomeric procyanidins fraction, which has demonstrated weak-to-moderate effects (Wonnemann et al 2001).

GABA receptor binding

SJW extracts have been shown to bind at GABA-A and -B receptors, to inhibit GABA reuptake, to evoke GABA release from synaptosomes and to exert an anxiolytic effect that is blocked by the benzodiazepine antagonist flumazenil (Perfumi et al 2002).

Upregulation of serotonin receptors

SJW significantly upregulates both 5-HT_{1A} and 5-HT_{2A} receptors and has a significant affinity for opiate sigma receptors, which may contribute to the antidepressant effect (Teufel-Mayer & Gleitz 1997).

Dopamine beta-hydroxylase inhibition

Studies on isolated constituents showed that hypericin and pseudohypericin can inhibit the enzyme dopamine beta-hydroxylase in vitro (Bilia et al 2002).

Inhibition of catechol-O-methyltransferase

This has been demonstrated in test tube studies (Thiede & Walper 1994).

Suppresses IL-6 synthesis

Various extracts from SJW produce a potent and dose-dependent inhibition of substance P-induced IL-6 synthesis (Fiebich et al 2001), which may also contribute to the herb's overall antidepressant effect.

Clinical note — Pharmacologically important constituents

It has generally been considered that most of the pharmacological activities of SJW are attributable to hypericin and the flavonoid constituent, hyperforin. Besides contributing to the antidepressant activity, hypericin is the primary constituent responsible for the photosensitivity reactions reported with high intakes. Hyperforin is also a major contributor to the herb's antidepressant activity (Butterweck et al 2003a, Mennini & Gobbi 2004) and considered the main constituent responsible for inducing the cytochrome P-glycoprotein and thereby producing drug interactions. Besides this, it demonstrates many other pharmacological effects such as antibacterial, anti-inflammatory and antineoplastic activities. Components previously considered void of activity have also been identified as important for pharmacological activity. For example, both procyanidin B2 and hyperoside increase the oral bioavailability of hypericin by 58% and 34%, respectively, and therefore, its clinical effects (Butterweck et al 2003b). A report published in June 2003 demonstrated that an extract devoid of both hyperforin and hypericin still exhibited antidepressant activity (Butterweck et al 2003a). Other constituents with antidepressant activity were identified and include hyperoside, isoquercitrin and miquelianin, and the 3-O-galactoside, 3-O-glucoside and 3-O-glucuronide of quercetin.

Monoamine oxidase (MAO) inhibition

Inhibition of MAO by hypericin demonstrated in vitro was believed to be the primary mode of action; however, this has not been confirmed in several subsequent studies that have shown only weak inhibitory activity at doses in excess of usual therapeutic levels (Di Carlo et al 2001).

Antiretroviral and antibacterial

Although in vitro and studies in animal models have identified antiretroviral activity for hypericin and pseudohypericin (Meruelo et al 1988), two clinical trials could not confirm these effects, even when larger doses of hypericin were administered (Gulick et al 1999, Jacobson et al 2001).

The mechanism involved is not known; however, it is suspected to involve direct inactivation of the virus or prevention of virus shedding, budding or assembly at the cell membrane (Meruelo et al 1988). The presence of light is an important requirement for antiretroviral activity to be demonstrated, as the effect appears to be photoactivated (Hudson et al 1993, Miskovsky 2002).

Hyperforin has also demonstrated antiviral and antibacterial activities (Medina et al 2006). Hyperforin exhibits effective antibacterial activity against methicillin-resistant *Staphylococcus aureus* (MRSA) and other gram-positive bacteria, but no growth-inhibitory effect on gram-negative bacteria or *Candida albicans* (Schempp et al 1999).

Anxiolytic

Several in vivo studies confirm the anxiolytic effects of SJW extract (Beijamini & Andreatini 2003, Jakovljevic et al 2000, Vandenbogaerde et al 2000). Activity at the GABA receptors and an increase in circulating GABA levels are likely to be involved.

Anti-inflammatory and analgesic

Both in vitro and in vivo testing has identified anti-inflammatory and analgesic activities for SJW (Jakovljevic et al 2000, Raso et al 2002). It potently inhibits binding to mu-, delta- and kappa-opioid receptors (Simmen et al 1998). In vivo tests also identify modulation of COX-2 expression for hypericum extract (Raso et al 2002). Studies with the isolated constituent hyperforin have shown that it potently inhibits COX-1 and 5-lipo-oxygenase in vitro (Albert et al 2002). Quercetin and other flavonoids contribute to the anti-inflammatory effect.

Anticancer effects

Hypericin, the photoactive compound of *Hypericum perforatum*, is probably the most powerful photosensitiser found in nature (Kacerovska et al 2008). It has minimal toxicity but exhibits potent photo-damaging effects in the presence of light (Olivo et al 2006). It is known to generate a high yield of singlet oxygen and other reactive oxygen species that are associated with photo-oxidative cellular damage. The application of photodynamic therapy (PDT) with hypericin for the treatment of cancers such as recurrent mesothelioma and skin cancer has been validated in clinical trials. It may also have potential as a photodynamic agent in the treatment of nasopharyngeal cancer (NPC) according to in vitro and in vivo models (Kacerovska et al 2008).

Hyperforin also exhibits antineoplastic potential based on the sum of its anticarcinogenic, antiproliferant, pro-apoptotic, anti-invasive and antimetastasic effects (Medina et al 2006). Hyperforin has been shown to effectively decrease the proliferation rates of a number of mammalian cancer cell lines, induce apoptosis of tumour cells and inhibit angiogenesis both in vitro and in vivo. Besides hypericin and hyperforin, polyphenolic procyanidin B2 has also demonstrated an inhibitory effect on the growth of leukaemia cells, brain glioblastoma cells and normal human astrocytes in vitro (Hostanska et al 2003). Further, the inhibitory effects on leukaemic cell growth were synergistically strengthened when hypericin and hyperforin were tested together.

Reduces alcohol intake

Several reports indicate comorbidity between depression and ethanol abuse and that depressive disorders and ethanol abuse may be associated with similar changes in the activity of central neurotransmitters (Markou et al 1998). In vivo studies using SJW in animal models of alcoholism have found that it does not alter food and water intakes, or the pharmacokinetics of alcohol, but a reduction in ethanol intake occurs (Panocka et al 2000).

Cognitive effects

SJW extracts and hyperforin improve cognitive function in experimental models (Kiewert et al 2004); however, clinical studies have been less convincing (Siepmann et al 2002, Timoshanko et al 2001). In vivo studies with hyperforin have found that it induces the release of acetycholine from cholinergic terminals in the hippocampus and striatum, providing an explanation for the observed effects. Preventive administration of *Hypericum perforatum* (350 mg/kg PO) counteracted the working memory impairments caused by repeated stress in male Wistar rats. The herb significantly improved hippocampus-dependent spatial working memory in comparison with control ($P < 0.01$) and alleviated some other negative effects of stress on cognitive functions (Trofimiuk & Braszko 2008).

> ***Clinical note — PDT for tumour cells***
> PDT involves the administration of a photosensitiser, which is taken up and stored within tumour cells, followed by light irradiation with a specific wavelength, giving rise to irreversible tissue destruction (Kacerovska et al 2008). It is aimed at destroying tumour cells without damaging surrounding normal tissues (Agostinis et al 2002). This combination approach results in the production of cytotoxic oxygen singlets within the tumour that cause irreversible cellular damage and tumour destruction.

Antispasmodic

SJW exhibits antispasmodic activity, according to research conducted with an experimental animal model (Jakovljevic et al 2000), most likely mediated via GABA activity.

Inhibits gastric motility

Among the chemical constituents of SJW extract tested, hyperforin and, to a lesser extent, the flavonoids kaempferol and quercitrin, inhibited acetylcholine-induced contractions in an animal model (Capasso et al 2008). SJW has a direct inhibitory effect on smooth muscle and could also possibly modulate gastric neurotransmission.

OTHER ACTIONS

No clinically significant effect on platelet aggregation has been identified (Beckert et al 2007)

Induction of CYP3A4 activity in the intestinal wall

Human studies have identified CYP3A4 and 2C19 induction effects for standard SJW extracts (e.g. LI 160), but no effects on CYP1A2, CYP2C9 or CYP2D6 (Durr et al 2000, Gurley et al 2008a, Jiang et al 2004, Wang et al 2001, 2004a). Human studies have failed to identify significant CYP3A4, 2D6, 2C9, 1A2 or 2C19 induction for low-hyperforin SJW extracts, such as ZE 117, using the appropriate probe drugs (Arold et al 2005, Madabushi et al 2006, Mueller et al 2004).

Hyperforin is a potent ligand for the pregnane X receptor, an orphan nuclear receptor that regulates expression of the CYP3A4 mono-oxygenase (Moore et al 2000). Although it is considered the chief constituent responsible for the pharmacokinetic interactions reported, there are other, less potent constituents in SJW, which also modulate cytochrome enzymes (Obach 2000).

Results from an open-label clinical study suggest that the effects of standard SJW (LI 160) on CYP3A4 enzymes may be biphasic, where the initial dose leads to a minor inhibition, followed by significant induction during long-term use (Rengelshausen et al 2005). Clinical studies indicate that CYP3A activity returns progressively to the basal level approximately 1 week after cessation of SJW administration (Imai et al 2008).

Increases levels of intestinal P-glycoprotein (P-gp)

SJW extract produced a 3.8-fold increase of intestinal P-gp expression in vivo (Durr et al 2000). Hyperforin has been identified as the key constituent responsible for P-gp induction effects (Tian et al 2005), although in vitro tests suggest other less potent constituents also exist such as quercetin, hypericin, biapigenin and kaempferol (Patel et al 2004, Weber et al 2004).

Once again, low-hyperforin SJW extracts do not appear to significantly induce P-gp (Arold et al 2005, Madabushi et al 2006, Mueller et al 2004).

In vitro and in vivo tests further indicate that P-gp effects caused by standard SJW (LI 160) are biphasic with an initial inhibitory effect followed by induction after longer exposure (Rengelshausen et al 2005, Wang et al 2004a).

CLINICAL USE

Up until recently, most trials conducted with SJW used a 0.3% hypericin water and alcohol extract known as LI 160. Subsequently, studies using different preparations, such as WS 5573 (standardised to hyperforin) or ZE 117 (a low concentration hyperforin preparation), have been tested.

Depression

There is now strong evidence from several meta-analyses to conclude that SJW extract is an effective treatment in mild, moderate and severe depressive disorder with efficacy comparable to tricyclic and selective serotonin reuptake inhibitor (SSRI) antidepressant drugs. Additionally, SJW is well tolerated and induces less adverse events than pharmaceutical antidepressants. There is also evidence indicating that it reduces relapse.

Mild-to-moderate depression

SJW has shown efficacy as a successful treatment for mild-to-moderate depression in numerous double-blind, placebo-controlled trials, confirmed by several meta-analyses.

The most recent Cochrane review released in 2005 analysed data from 37 double-blind, randomised studies (n = 4925) that used monopreparations of SJW over a treatment period of at least 4 weeks (Linde et al 2005). It concluded that hypericum extracts improved symptoms more than placebo and produced effects similar to synthetic antidepressants (tricyclics and SSRIs) in adults with mild-to-moderate depression.

This confirms the results obtained in two earlier meta-analyses (Linde & Mulrow 2000, Whiskey et al 2001).

Subsequently, a double-blind study of 388 patients with moderate depression has found SJW extract (900 mg daily of extract STW3-VI) to be as effective as citalopram (20 mg daily) ($P < 0.0001$) (Gastpar et al 2006). The HDS scores were reduced to 10.3 ± 6.4 for SJW extract, 10.3 ± 6.4 for citalopram and 13.0 ± 6.9 for placebo and both antidepressants were significantly more effective than placebo. At the end of treatment, 54.2% of the SJW group and 55.9% of the citalopram group were assessed as responders compared with 39.2% for placebo. With regard to safety, significantly more adverse events were documented in the

Clinical note — The Hamilton Depression Scale (HDS)

The HDS is an observer-rated scale that focuses mainly on somatic symptoms of depression. Although the original version included 21 items, a similar version using 17 items is more commonly used in clinical trials. Most studies using the HDS report the number of 'treatment responders' (patients achieving a score less than 10 and/or less than 50% of the baseline score) (Linde et al 2005).

citalopram group (53.2%) than for SJW (17.2%) or placebo (30%).

Kasper et al re-analysed data from of a subset of patients ($n = 217$) suffering from an acute episode of mild depression from controlled trials testing SJW extract WS 5570 (Kasper et al 2008a). The analysis shows that SJW extract WS 5570 has a meaningful beneficial effect during acute treatment of patients suffering from mild depression and leads to a substantial increase in the probability of remission. The studies tested three different doses, 600, 900, or 1200 mg/day or placebo for 6 weeks. Patients receiving active treatment with WS 5570 experienced decreases in the Hamilton depression scale (HDS) total score by an average of 10.8 (600 mg/day), 9.6 (900 mg/day), and 10.7 (1200 mg/day) points between the pretreatment baseline value and the end of acute treatment, compared to 6.8 points in the placebo group. All differences were significant. The rates of responders were 73%, 64%, 71% and 37% for WS 5570 600 mg/day, 900 mg/day and 1,200 mg/day and placebo, respectively.

Paediatric use

Results from a postmarketing surveillance study of 101 children under 12 years with mild-to-moderate depression has suggested that SJW may be an effective and well-tolerated treatment in this population (Hubner & Kirste 2001). The number of physicians rating effectiveness of treatment with SJW as 'good' or 'excellent' was 72% after 2 weeks, 97% after 4 weeks and 100% after 6 weeks and ratings by parents were similar. Although encouraging, it is difficult to interpret the clinical significance of the results, as there was no placebo group and the final evaluation included only 76% of the initial sample.

An 8-week open pilot study was conducted with SJW (300 mg three times daily) in 26 adolescents with major depressive disorders (MDDs) (Simeon et al 2005). The subjects were aged 12–17 years (mean, 14.8 years). Only 11 patients completed the study of which 9 (82%) showed significant clinical improvement based on Clinical Global Improvement change scores. Once again, interpretation of these results is hampered by a large drop-out rate.

Preventing relapse of depression

A double-blind, placebo-controlled, multicentre trial conducted by Kasper et al evaluated the efficacy and safety of hypericum extract WS 5570 in preventing relapse during 6 months' continuation treatment and 12 months' long-term maintenance treatment after recovery from an episode of recurrent depression (Kasper et al 2008b). After 6 weeks of single-blind treatment with 3 × 300 mg/day WS 5570 patients with score ≤2 on item 'Improvement' of the Clinical Global Impressions (CGI) scale and a HDS total score decrease ≥50% versus baseline were randomised to 3 × 300 mg/day WS 5570 or placebo for 26 weeks. This provided a total of 426 patients in the next study phase. Treatment with WS 5570 showed more favourable HDS and Beck Depression Inventory time courses and greater overall improvement (CGI) than controls. In long-term maintenance treatment, a pronounced prophylactic effect of WS 5570 was observed in patients with an early onset of depression as well as in those with a high degree of chronicity. Adverse event rates under WS 5570 were comparable to placebo.

Clinical note — Low hyperforin extracts effective?

Considering that hyperforin demonstrates significant antidepressant activity, it is important to evaluate whether low-hyperforin-containing SJW preparations remain effective. Three randomised, double-blind studies that have compared low-hyperforin extracts (ZE 117) to fluoxetine or imipramine suggest that the absence of hyperforin does not hinder the antidepressant effect (Friede et al 2001, Schrader 2000, Woelk 2000).

Major depression

Although a 2005 Cochrane review stated that SJW shows only minimal benefits over placebo in major depression (Linde et al 2005) an updated 2008 Cochrane systematic review has concluded that hypericum extracts: (a) are superior to placebo in patients with major depression; (b) are similarly effective as standard antidepressants (SSRIs and tricyclics); and (c) have fewer side effects than standard antidepressants (Linde et al 2008). A total of 29 randomised trials were evaluated ($n = 5489$), including 18 comparisons with placebo and 17 comparisons with synthetic standard antidepressants. The standard antidepressants used as active comparators were fluoxetine (6 trials, dosage 20 to 40 mg), sertraline (4 trials, 50–100 mg), imipramine (in 3 trials, dosage 100–150 mg), citalopram (1 trial, 20 mg), paroxetine (1 trial, 20–40 mg), maprotiline (1 trial, 75 mg) and amitriptyline (1 trial, 75 mg). Most trials used a dose range 500 mg–1200 mg/day of SJW.

This result is clinically important as the effects of standard antidepressants over placebo are modest and although SSRIs are better tolerated than older antidepressant drugs (such as MAOIs), side effects are still common.

Comparisons to SSRI drugs in major depression

A meta-analysis compared the efficacy and tolerability of hypericum with SSRIs as a group of standard antidepressants. Thirteen randomised, placebo-controlled clinical trials were included in the analysis, which found that hypericum does not differ from SSRIs according to efficacy and adverse events in MDD. Hypericum was better tolerated, as there were lower withdrawal rates due to adverse events by hypericum, which is an advantage in management of MDD (Rahimi et al 2009).

Commission E approves the use of SJW for psychovegetative disturbances, depressive moods, anxiety and nervous unrest (Blumenthal et al 2000).

Obsessive-compulsive disorder

Treatment with a fixed dose of 450 mg of SJW containing 0.3% hypericin twice daily over 12 weeks improved the condition in 5 of 12 patients,

Clinical note — Relative safety of SJW compared with pharmaceutical antidepressants

Much has been made of the known or suspected risks associated with the use of SJW, with far too little discussion focusing on the decisive question of its relative safety compared with pharmaceutical antidepressants. It has been estimated that approximately 1 in 30,000 people using SJW will experience an adverse reaction, including those attributed to drug interactions (Schulz 2006). An overview of 16 postmarketing surveillance studies involving different SJW preparations and 34,804 patients found that side-effect incidence varied from 0 to 2.8% in short-term studies (4–6 weeks) and 3.4–5.7% in long-term studies (52 weeks) (Linde & Knuppel 2005). Gastrointestinal symptoms, sensitivity to light and other skin conditions and agitation were the most commonly reported side effects and were generally described as mild. The review found that serious side effects or interactions were not reported by any study. Taking this into account, the incidence of side effects to SJW is approximately 10-fold lower than for conventional antidepressants (SSRIs) (Schulz 2006). The most common adverse event among spontaneous reports is photosensitivity, which is estimated to occur in 1 in 300,000 treated cases. This can occur with a dose of 5–10 mg/day hypericin, which is 2–4-fold higher than the recommended dose. SJW has no significant effect on blood pressure or heart rate (Siepmann et al 2002), making it a safer choice than tricyclic antidepressants in patients with cardiovascular disease. It also lacks atropinic activity, so side effects such as dry mouth, urinary retention and blurred vision do not occur. In addition, the common side effects reported for SSRIs, such as anorexia, insomnia, sexual dysfunction, excessive sweating and visual disturbance, have not been reported for SJW. Similar to all standard antidepressants, SJW can interact with other medicines and needs to be judiciously prescribed.

according to an open study (Taylor & Kobak 2000).

Seasonal affective disorder (SAD)

Wheatley found that people with mild-to-moderate SAD experienced significant improvements with anxiety, loss of libido and insomnia after 8 weeks' treatment with SJW (Wheatley 1999). The test group receiving SJW extract (Kira 300 mg) three times daily plus light therapy experienced superior sleep compared with the group receiving SJW as stand-alone treatment.

Polyneuropathy

Although SJW is sometimes used for nerve pain, a randomised, double-blind, crossover study of 54 patients identified a trend towards lower total pain score with SJW treatment, although none of the individual pain ratings were significantly changed (Sindrup et al 2001). The dose of SJW used provided 2.7 mg/day total hypericin and was taken over 5 weeks.

Menopause: psychological and psychosomatic symptoms

In at least one trial, SJW has been investigated as sole therapy in menopausal and premenopausal women with psychological and psychosomatic symptoms. After 12 weeks' treatment with 900 mg hypericum (Kira 300 mg three times daily) symptoms diminished or disappeared completely in the majority of women (76.4% by patient evaluation and 79.2% by physician evaluation). Interestingly, sexual wellbeing also improved in 80% of cases (Grube et al 1999).

In combination

Another study investigated a fixed combination of isopropanolic black cohosh (Remifemin; standardised to 1 mg triterpene glycosides) and ethanolic SJW (standardised to 0.25 mg total hypericin) in 301 women with menopausal symptoms with pronounced psychological symptoms (Uebelhack et al 2006). The double-blind, randomised study found that 16 weeks of herbal treatment produced a significant 50% reduction in the Menopause Rating Scale score compared to 20% with placebo and a significant 42% reduction in the HDS score compared to only 13% in the placebo group.

A second study testing the effectiveness of combined SJW and black cohosh found that combination therapy was superior to stand-alone black cohosh therapy for the treatment of climacteric mood symptoms in general practice (Briese et al 2007). This was a prospective, controlled, open-label observational study which involved 6141 women attending 1287 outpatient gynaecologists in Germany.

Perimenopause

Symptomatic perimenopausal women aged 40–65 years who experience hot flushes (three or more per day) may experience significant improvements to menopause-specific quality of life using SJW extract (900 mg t.i.d.) according to a double-blind, placebo-controlled study (Al-Akoum et al 2009). After 3 months of treatment, herbal treatment was significantly better than placebo for menopause-specific quality of life and also provided significant improvements for self-reported sleep problems. No significant effects were seen at 6 weeks indicating that the effects have slow onset.

Premenstrual syndrome (PMS)

An open study in patients with PMS found that a low dose of 300 mg SJW daily produced significant reductions in all outcome measures. The degree of improvement in overall PMS scores between baseline and the end of the trial was 51%, with over two-thirds experiencing at least a 50% decrease in symptom severity (Stevinson & Ernst 2000).

Herpes infection
Based on its antiviral activity, SJW is also used clinically in the treatment of herpes virus infections. One study of unknown design found that oral extract LI 160 (over a period of 3 months) reduced the frequency and severity of episodes of recurrent herpes labialis and herpes genitalis (Mannel et al 2000).

Smoking cessation
Preliminary evidence from experimental models suggests that SJW may be of use in reducing nicotine withdrawal signs. In the study, SJW significantly and dose-dependently reduced the total nicotine abstinence score (Catania et al 2003). Further studies are required to determine its usefulness for smoking cessation treatment in humans.

Topical use

Atopic dermatitis
A cream containing SJW extract (standardised to 1.5% hyperforin) was shown to reduce the intensity of eczematous lesions when used twice daily in a prospective, double-blind study (Schempp et al 2003a). Beneficial effects were already observed at the first review, which was on day 7.

Treatment of acute and contused injuries
No controlled studies are available, but anti-inflammatory, analgesic and bactericidal activities provide a theoretical basis for its use.

Commission E approves the topical use of oily SJW preparations for this indication (Blumenthal et al 2000).

Myalgia
Although no controlled studies are available, anti-inflammatory and analgesic activities provide a theoretical basis for its use in this condition.

Commission E approves the topical use of oily SJW preparations for this indication (Blumenthal et al 2000).

First-degree burns
Although no controlled studies are available, anti-inflammatory, analgesic and bactericidal activities provide a theoretical basis for its use in this condition.

Commission E approves the topical use of oily SJW preparations for this indication (Blumenthal et al 2000).

PDT
A prospective study aimed at investigating the efficacy of PDT with topical application of an extract of *H. perforatum* in actinic keratosis, basal cell carcinoma (BCC) and morbus Bowen (carcinoma in situ) was conducted with 34 patients (8 with actinic keratoses (AKs), 21 with BCC and 5 with Bowen's disease) (Kacerovska et al 2008). Hypericum extract was applied on the skin lesions under occlusion and followed by irradiation with 75 J/cm^2 of red light 2 h later. The treatment was performed weekly for 6 weeks on average. The percentage of complete clinical response was 50% for AKs, 28% in patients with superficial BCC and 40% in patients with Bowen's disease. There was only a partial remission seen in patients with nodular BCCs. A complete disappearance of tumour cells was found in the histologic preparation of 11% of patients with superficial BCCs and 80% in the patients with Bowen's disease. Unfortunately, the combined treatment was poorly tolerated as all patients complained of burning and painful sensations during irradiation.

Attention deficit hyperactive disorder (ADHD)
A randomised, double-blind, placebo-controlled trial found that SJW (300 mg three times daily of *H. perforatum* standardised to 0.3% hypericin) was ineffective for the symptomatic treatment of ADHD in children (Weber et al 2008). The study involved 54 children aged 6–17 years who met Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition) criteria for ADHD by structured interview and was conducted over 8 weeks.

OTHER USES
In practice, SJW is also used to treat fibrositis, nervous exhaustion, sciatica and gastrointestinal conditions, such as oesophagitis and peptic ulcers. Traditionally, SJW has been used for wound healing, diuretic, melancholy, pain relief, treatment for snake bites, bedwetting in children, malaria and psychosis.

DOSAGE RANGE
- Dried herb: 2–5 g/day.
- Liquid extract (1:2): 3–6 mL/day.
- Tincture (1:5): 7.5–15 mL/day.
- Standardised extract containing 1.0–2.7 mg total hypericin daily.
- It is advised that patients using SJW long term should have their doses reduced slowly when discontinuing its use.

External use
- Oily macerate: Macerate flowering tops in olive oil for several weeks and stir often, then drain through a gauze. Store in a dark bottle out of direct light. Apply oil directly to the affected area. To promote extraction of flavonoids, store in a sunny area for 6 weeks (oil will turn red).

According to clinical studies
Doses are for dried herb or equivalent.
- Mild-to-moderate depression: adult — doses ranging from 350–1800 mg/day have been used; children (aged 6–12 years) — 200–400 mg/day in divided doses.

  The extract most often studied is LI 160, although others have also been tested, such as WS 5573 (standardised to hyperforin), ZE 117 (a low concentration hyperforin preparation), WS 550 and STW3-V1.
- Major depression: 500 mg–1800 mg/day in divided doses.
- Obsessive compulsive disorder (OCD): 450 mg twice daily of an extract containing 0.3% hypericin.
- Menopausal symptoms: 900 mg/day in divided doses.

- PMS: 300 mg/day (standardised to 900 microgram hypericin).
- SAD: 900 mg/day in divided doses.

ADVERSE REACTIONS

It has been estimated that approximately 1 in 30,000 people using SJW will experience an adverse reaction, including those attributed to drug interactions (Schulz 2006). The incidence of side effects to SJW is approximately 10-fold lower than for conventional antidepressants (SSRIs). According to an overview of 16 post-marketing surveillance studies, gastrointestinal symptoms, sensitivity to light and other skin conditions and agitation were the most commonly reported side effects and were generally described as mild (Linde & Knuppel 2005).

Photosensitivity (unlikely at therapeutic doses)

The most common adverse event among spontaneous reports is photosensitivity, which is estimated to occur in 1 in 300,000 treated cases. This can occur with a dose of 5–10 mg/day hypericin, which is 2–4-fold higher than the recommended dose. Commission E has noted the possibility of photosensitivity reactions, particularly in fair-skinned people.

SIGNIFICANT INTERACTIONS

SJW is one of the few herbal medicines that has been subjected to controlled studies in order to determine the significance of its interaction with numerous drugs. Although this can be reassuring, the clinical significance of many interactions is still unpredictable because of the variable chemical composition of products.

It is important to note that interactions due to CYP and P-gp induction do not appear clinically significant with low-hyperforin extracts (ZE 117). This was recently confirmed in a clinical study testing SJW powder with low hyperforin content which was shown to cause a mild induction of CYP3A which was not considered clinically relevant (Mueller et al 2009).

Clinical note — Mechanisms responsible for reported interactions

Based on the herb's pharmacology, there are several mechanisms by which it may interact with drugs. Considering that SJW has significant serotonin reuptake inhibitor activity and significantly upregulates both 5-HT_{1A} and 5-HT_{2A} receptors, concomitant use of drugs that elevate serotonin levels, such as tricyclic antidepressants or SSRIs, may result in additive or synergistic effects and increase the risk of serotonergic syndrome. As the constituent hyperforin has a significant and selective induction effect on CYP3A4 and 2C19 activity (Durr et al 2000, Wang et al 2001) and induces the drug transporter P-gp, a number of pharmacokinetic interactions are possible with those drugs that are substrates for CYP3A4 or 2C19 and/or rely on P-gp transport. Refer to Chapter 8 for further information on interactions with herbs and natural supplements.

Alprazolam

Decreases serum levels of alprazolam via CYP induction. Monitor for signs of reduced drug effectiveness and adjust the dose if necessary or avoid.

Amitriptyline

Although SJW decreases serum levels of amitriptyline via CYP induction in vivo (Johne et al 2002), theoretically it could also induce increases in serotonin availability, which has an opposite effect; the clinical outcome of these two interacting mechanisms is unknown — monitor for signs of changed drug effectiveness and adjust the dose if necessary or avoid concurrent use.

Antidepressants (SSRIs and SNRIs)

Increased risk of serotonin syndrome possible; however, increased antidepressant activity is also possible with appropriate doses — avoid concurrent use unless under medical supervision, so that doses may be altered appropriately.

Anticonvulsants

Phenobarbitone, phenytoin: SJW may increase drug metabolism resulting in reduced drug efficacy — avoid concurrent use unless under medical supervision, so that doses may be altered appropriately.

Antineoplastic drugs

Irinotecan (Mathijssen et al 2002), imatinib mesylate etc. which are P-gp and/or CYP3A4 substrates — avoid (see Chapter 10 for more information on safety of complementary medicines and cancer).

Atorvastatin

SJW reduces the efficacy of atorvastatin, so lipid-lowering effects are compromised, according to a clinical study which tested a product called Movina (containing 300 mg of *Hypericum perforatum*) taken as one tablet twice daily (Andren et al 2007).

Cisplatin

Cisplatin-induced histological abnormality of the kidney was blocked by pretreatment with SJW in vivo (Shibayama et al 2007). Total and free cisplatin concentration in serum was not influenced by SJW treatment suggesting that this may be a beneficial interaction under professional supervision.

Cyclosporin

Decreases plasma levels of cyclosporin significantly within 3 days of concomitant use via CYP induction (Bauer et al 2003) — avoid concurrent use.

A pharmacokinetic study with kidney graft recipients suggests that the effect is not significant when low-hyperforin products are used (Madabushi et al 2006).

Digoxin

Decreases serum digoxin levels significantly within 10 days of concomitant use (Johne et al 1999), chiefly due to induction of the P-gp. The

interaction between digoxin and SJW in humans has been confirmed more recently by Gurley et al and is clinically significant (Gurley et al 2008b) — monitor patient for signs of reduced drug effectiveness and adjust the dose if necessary or avoid concurrent use.

Gliclazide
Treatment with SJW significantly increases the apparent clearance of gliclazide, which is independent of CYP2C9 genotype, according to a crossover clinical study (Xu et al 2008). People with diabetes receiving this combination should be closely monitored to evaluate possible signs of reduced efficacy.

HIV non-nucleoside transcriptase inhibitors
Decreases serum levels — avoid concurrent use.

HIV protease inhibitors
Decreases serum levels — avoid concurrent use.

Methadone
Decreases serum levels via CYP induction — avoid concurrent use (Eich-Hochli et al 2003).

Midazolam
Decreases serum levels of midazolam via CYP induction — monitor for signs of reduced drug effectiveness and adjust the dose if necessary or avoid.

Nifedipine
SJW was shown to induce nifedipine metabolism in vivo (Wang et al 2007) — monitor for signs of reduced drug effectiveness and adjust the dose if necessary or avoid.

Omeprazole
Decreases serum levels via CYP induction (Wang et al 2004b) — monitor for signs of reduced drug effectiveness and adjust the dose if necessary or avoid.

Oral contraceptives
Breakthrough bleeding has been reported, which can indicate decreased effectiveness of oral contraceptives. In 2003, a controlled study confirmed that standard doses of SJW cause an induction of ethinyl oestradiol–norethindrone metabolism consistent with increased CYP3A activity (Hall et al 2003) — use this combination with caution.

In 2002, a pharmacokinetic study found no significant interaction between low-hyperforin SJW and low-dose oral contraceptives (Madabushi et al 2006). This has been confirmed in a further clinical study using a SJW extract (Ze 117) with low hyperforin content on the pharmacokinetics of ethinylestradiol and 3-ketodesogestrel (Will-Shahab et al 2009) — low-hyperforin extracts appear to be safe.

PUVA therapy
High-dose hypericin may increase sensitivity to UV radiation — caution is advised.

Simvastatin
Decreases serum levels of simvastatin via CYP induction (Sugimoto et al 2001) — monitor for signs of reduced drug effectiveness and adjust the dose if necessary (no interaction is expected with pravastatin).

Tacrolimus
Decreases serum levels of tacrolimus via CYP induction (Mai et al 2003) — avoid this combination.

Verapamil
Decreases serum levels of verapamil via CYP induction — monitor for signs of reduced drug effectiveness and adjust the dose if necessary.

Warfarin
Metabolism of warfarin is chiefly by CYP2C9, and a minor metabolic pathway is CYP3A4, so theoretically it may interact with SJW. A clinical study found no change to international normalised ratio (INR) or platelet aggregation (Jiang et al 2004), but there are case reports suggesting that SJW may lower the INR. Caution is advised — monitor INR.

CONTRAINDICATIONS AND PRECAUTIONS
People with fair skin undergoing UV treatment should use high doses of SJW with caution.

PREGNANCY USE
A systematic review of the literature for evidence on the use, safety and pharmacology of SJW focusing on issues pertaining to pregnancy found there is in vitro evidence from animal studies that SJW during pregnancy does not affect cognitive development nor cause long-term behavioural defects, but may lower offspring birth weight (Dugoua et al 2006). Although encouraging, safe doses in pregnant women have not yet been determined. In practice, it is not used in pregnancy.

SJW appears to be relatively safe in lactation (Dugoua et al 2006). A study of breastfeeding mothers indicated that low levels of hyperforin are excreted into breast milk; however, infant exposure is comparable to levels reported in most studies assessing antidepressants or neuroleptics and no side effects were seen in the mothers or infants (Klier et al 2006). The doses used were 300 mg of SJW (LI 160, three times daily).

PATIENTS' FAQs
What will this herb do for me?
SJW is an effective treatment for mild, moderate and severe depression and it reduces the risk of relapse. Its antidepressant effects are similar to pharmaceutical antidepressant drugs; however, it is better tolerated with less side effects. It may also be useful for PMS symptoms, SAD, OCD and for menopausal and premenopausal women with psychological and psychosomatic symptoms. The oily preparations are also used topically to treat burns, injuries, allergic dermatitis and muscle pain.

When will it start to work?
It often starts to exert beneficial effects in depression within 2–4 weeks of continuous use; however, maximal effects in other conditions may take longer.

Are there any safety issues?

SJW is well tolerated and has far less side effects than pharmaceutical antidepressant drugs, but it can interact with a number of different medications. Patients with clinically diagnosed depression should be under the care of a healthcare professional.

PRACTICE POINTS/PATIENT COUNSELLING

- SJW contains numerous constituents with pharmacological activity, including antidepressant, analgesic, anti-inflammatory, antispasmodic, anxiolytic, antineoplastic, antiviral and bactericidal activities.
- Numerous clinical studies support the use of SJW as an effective treatment for mild, moderate and severe depression. The most commonly studied extract is LI 160 although others have also been tested (e.g. WS 5573 (standardised to hyperforin), ZE 117 (a low concentration hyperforin preparation), WS 550 and STW3-V1). Clinical effects are comparable to tricyclic antidepressants and SSRIs; it also reduces the incidence of depression relapse.
- With regard to safety, SJW is better tolerated than standard antidepressants (SSRIs and tricyclics); however, it still needs to be prescribed judiciously to avoid interactions. Patients with clinically diagnosed depression should be under the care of a healthcare professional.
- Low-hyperforin-containing SJW extracts do not have the same interaction potential as standard SJW extracts and may present a safer option for some individuals.
- Preliminary human studies have suggested a possible role in PMS, SAD, OCD and in menopausal and premenopausal women with psychological and psychosomatic symptoms.
- Oily preparations have been used topically to treat burns, acute and contused injuries, atopic dermatitis and myalgia.

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St Mary's thistle

HISTORICAL NOTE St Mary's thistle has a long history of traditional use since ancient times. Over the centuries, it has been touted as a remedy for snakebite, melancholy, liver conditions and promoting lactation. The name 'milk thistle' derives from its characteristic spiked leaves with white veins which, according to legend, were believed to carry the milk of the Virgin Mary.

OTHER NAMES

Carduus marianus, cardo blanco, cardo de burro, chandon marie, holy thistle, lady's milk, lady's thistle, Mariendistel, Marian thistle, Mary thistle, milk thistle, silybum, true thistle.

BOTANICAL NAME/FAMILY

Silybum marianum (family [Compositae] Asteraceae)

PLANT PART USED

Ripe seed

CHEMICAL COMPONENTS

Often silymarin is referred to as the active constituent of seeds from St Mary's thistle, but in fact it is a complex of at least seven flavonolignans. The principal component of silymarin is silybin (also referred to as silibinin), which makes up more than 50% of silymarin and is regarded as one of the most biologically active constituents (Jacobs et al 2002). Silybin is not a single compound either, but rather a mixture of two diastereoisomers, silybin A and silybin B (Kroll et al 2007). Other flavonolignans include isosilybin, silychristin and silydianin, all of which exist as diastereoisomers. A new flavonolignan, silyamandin, was discovered in St Mary's thistle preparations (MacKinnon et al 2007). St Mary's thistle seeds also contain a fixed oil comprising linoleic, oleic and palmitic acids, tocopherol and sterols, including cholesterol, campesterol, stigmasterol and sitosterol.

Schrieber et al found that the pharmacokinetics of silymarin was altered in patients with hepatitis C and non-alcoholic liver disease compared with healthy volunteers in a way that it correlates with highest caspase-3/7 activity (a measure of disease activity) (Schrieber et al 2008). Formulation research in dogs showed that the bioavailability of solid dispersion pellets is five times higher than that of a poorly water-soluble milk thistle extract (Sun et al 2008). Another in vivo study reported that a phytosome complex of phosphatidylcholine and silybin showed markedly enhanced bioavailability (Filburn et al 2007).

MAIN ACTIONS

Most investigation has used standardised preparations of St Mary's thistle, the silymarin constituent group or silybin.

Hepatoprotective effect

Protection of liver cells has been demonstrated against the following substances in vitro or in vivo:

- Carbon tetrachloride-induced liver cirrhosis (Chrungoo et al 1997, Mourelle et al 1989, Muriel & Mourelle 1990, Tsai et al 2008).
- Ethanol (Das & Vasudevan 2006).
- Paracetamol-induced liver peroxidation (Chrungoo et al 1997, Muriel et al 1992).
- Cyclosporin (von Schonfeld et al 1997).
- Phenothiazine (Palasciano et al 1994).
- Butyrophenone (Palasciano et al 1994).
- Erythromycin (Davila et al 1989).
- Amitriptyline and nortriptyline (Davila et al 1989).
- Oestradiol (Morazzoni & Bombardelli 1995).
- *Amanita phalloides* (Floersheim 1976, Vogel et al 1984).
- Tacrine (Galisteo et al 2000).
- Iron overload (Masini et al 2000, Pietrangelo et al 1995).
- Benzo(a)pyrene induced lung cancer (Kiruthiga et al 2007).

The exact mechanism of action has not been fully elucidated; however, several observations have been made which suggest that toxin blockade, antioxidant and free radical scavenging effects are among the most likely modes of actions. A study suggests that silymarin may be effective in protecting hepatocytes from saturated fatty acids-induced cell death (Song et al 2007).

Toxin blockade

Silymarin and silybin alter the structure of hepatocyte cell membranes by being incorporated into the hydrophobic–hydrophilic interface of the microsomal bilayer (Parasassi et al 1984). Silybin interacts with the surface rather than deeper regions of the bilayer, and therefore does not change significantly the biophysical properties of the deeper membrane regions (Wesolowska et al 2007). Additionally, inhibition of cyclic adenosine monophosphate (AMP)-dependent phosphodiesterase by silybin has been shown in vitro, which results in increased cAMP and stabilisation of lysosomal membranes (Koch et al 1985). Both actions alter cell membrane function and may be important for protecting the cell from toxin-induced damage. Alternatively, components in St Mary's thistle may bind to the hepatocyte cell membrane receptor site and inhibit binding of toxins to these sites (Jacobs et al 2002).

Chelates iron

Hepatic iron toxicity and fibrosis due to iron overload are mediated by lipid peroxidation of biological membranes and the associated organelles (Masini et al 2000). Both silymarin and silybin demonstrate protective effects against hepatic iron toxicity in vivo, primarily owing to antioxidant mechanisms. However, there is some evidence that iron chelation may also be involved (Borsari et al 2001, Masini et al 2000, Pietrangelo et al 1995, Psotova et al 2002). Serum ferritin levels, but not serum iron and transferring-iron saturation, were significantly decreased in patients with hepatitis C and Batts–Ludwig fibrosis stages II, III or IV following 12 weeks of treatment with silybin and soy phosphatidylcholine complex (IdB 1016). Stage III or IV fibrosis was independently associated with decreased post-treatment serum ferritin level (Bares et al 2008).

Liver regeneration/liver preservation

Silymarin accelerates the regeneration of hepatocytes after liver damage, according to an in vivo study. Silymarin was shown to increase hepatocyte protein synthesis by stimulating the activity of ribosomal RNA polymerase (Kropacova et al 1998). One study using isolated rat livers investigated whether silybin exerts protective effects in liver transplantation injury. It was found that liver preservation done in the presence of silybin improved parameters affected by preservation and reperfusion, thus it increased adenosine triphosphate (ATP) and decreased oxidative stress to values observed in livers which had never been preserved nor re-perfused. This points towards a potential use of silybin in liver transplantation surgery (Ligeret et al 2008).

Following silymarin treatment of liver fibrosis induced by carbon tetrachloride in rats, elevated levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP) were decreased (Tsai et al 2008).

Antioxidant effect

Several constituents found in St Mary's thistle have demonstrated antioxidant and free radical scavenging activity in a variety of models. Silymarin exerts both a direct and an indirect free radical scavenging activity, increasing the redox state and total glutathione content of the liver, intestine and stomach in vivo (Gonzalez-Correa et al 2002, Hagymasi et al 2002, Liu et al 2001, Valenzuela et al 1989). Other studies have shown that silymarin regenerates antioxidant enzymes (Kiruthiga et al 2007), but to a lesser extent than ascorbic acid (Das & Vasudevan 2006). The observed antioxidant activity of silymarin is dose dependent (Asghar & Masood 2008). Silybin fully alleviates the rise in metabolic flow driven radical oxygen species (ROS) formation in concentrations as low as 10 μm, which is particularly important in pathological conditions where the generation of mitochondrial ROS is significantly increased (Detaille et al 2008). Moreover, antioxidant and free radical scavenging activities inhibited the generation of oxidised LDL and subsequent scavenger receptor-dependent monocyte adhesion (Wallace et al 2008). Silydianin has shown to activate caspase-3, to stabilise cell membranes and to scavenge free radicals (Zielinska-Przyjemska & Wiktorowicz 2006).

Anti-inflammatory

The anti-inflammatory activity of silymarin is due to several different mechanisms, such as antioxidant and membrane-stabilising effects, and inhibition

of the production or release of inflammatory mediators, such as arachidonic acid metabolites. Inhibitory activity on lipo-oxygenase, cyclo-oxygenase (COX) and prostaglandin (PG) synthetase has been demonstrated in several in vitro assays and animal studies (Alarcon de la Lastra et al 1992, Dehmlow et al 1996, Fiebrich & Koch 1979, Rui et al 1990, Zhao et al 1999). Furthermore, silymarin inhibits NF-kappaB signalling and suppresses tumour necrosis factor (TNF)-alpha, nitric oxide synthase (iNOS) and interleukin (IL)-1 (Agarwal et al 2006, Polyak et al 2007).

Brain- and cardioprotective effect

Silymarin has been shown to reduce sepsis-induced lung and brain injury, partially through its antioxidant effects, inhibition of neutrophil infiltration and regulation of inflammatory mediator release (Nencini et al 2007, Toklu et al 2008).

Furthermore, silybin has protected rat cardiac myocytes against isoproterenol-induced injury by restarting mitochondrial function and upregulating the expression of SIRT1 and anti-apoptotic Bcl-2 family proteins (Zhou et al 2006a, 2006b). A subsequent study by the same authors found that the cardiac myocytes were protected against isoproterenol-induced DNA damage by silybin via the caspase-3 pathway and downregulation of p53 phosphorylation (Zhou et al 2006a, 2006b). Thus, silybin seems to exert anti-apoptotic (cell death preventing) properties.

Nephroprotective effect

In vitro experiments with kidney cells damaged by paracetamol, cisplatin or vincristin demonstrate that administration of silybin before or after the chemical-induced injury can lessen or avoid the nephrotoxic effects (Sonnenbichler et al 1999). Animal studies have confirmed the nephroprotective effect for cisplatin-induced injury (Karimi et al 2005). In one study, the effects of cisplatin on glomerular and proximal tubular function as well as proximal tubular morphology were totally or partly ameliorated by silybin (Gaedeke et al 1996). In an in vivo study, silymarin significantly decreased gentamicin-induced nephrotoxicity when used as a single agent and when used in combination with vitamin E in comparison to the placebo group. Serum creatinine concentrations, but not urea concentrations, were significantly lower (Varzi et al 2007).

Gastroprotective effect

St Mary's thistle extract produces a dose-dependent antiulcerogenic activity against indomethacin-induced ulcers, which can be histologically confirmed, according to research with test animals (Khayyal et al 2001). This is associated with reduced acid output, increased mucin secretion, increased PGE_2 release and decreased leukotriene release. Experiments with silymarin have found it to be effective in the prevention of gastric ulceration induced by cold-restraint stress in rats (Alarcon de la Lastra et al 1992) and post-ischaemic gastric mucosal injury (Alarcon de la Lastra et al 1995).

In combination

A herbal formulation known as STW 5, containing extracts of milk thistle fruit and eight other herbs (bitter candy tuft, lemon balm leaf, chamomile flower, caraway fruit, peppermint leaf, licorice root, angelica root and greater celandine) produced antiulcerogenic activity against indometacin-induced gastric ulcers in rats as well as antisecretory and cytoprotective activities (Khayyal et al 2001). In a newer study, it was shown that STW 5 lowered the gastric acidity as effectively as commercial antacid preparations (i.e. Rennie, Talcid, Maaloxan), prevented secondary hyperacidity more effectively and, additionally, inhibited serum gastrin levels in rats (Khayyal et al 2006).

Antidiabetic effect

Silybin lowered glucose production from various gluconeogenic substrates in perifused rat hepatocytes. Silybin also reduced glycolysis from carbohydrates in a cell perifusion system in a dose-dependent manner via an inhibitory effect on pyruvate kinase activity. Furthermore, a dramatic effect upon oxidative phosphorylation was shown and illustrated by a decrease in ATP-to-adenosine diphosphate (ADP) ratio and an increase in lactate-to-pyruvate ratio (Detaille et al 2008).

Antiviral effect

In an in vitro study, a standardised St Mary's thistle extract (MK-001) and other commercial St Mary's thistle preparations combined with interferon-alpha inhibited hepatitis C virus (HCV) replication more than when interferon-alpha was given alone. Silybin A and B as well as isosilybin A and B displayed the strongest effects (Polyak et al 2007). Interestingly, milk thistle has no direct antiviral activity, but rather has protective effects in the inflammatory response to HCV, thereby supporting antiviral treatment in this disease (Torres et al 2004).

Mast-cell stabilisation

Silybin has shown mast-cell-stabilisation activity in vivo (Lecomte 1975), which was confirmed some years later and found to be dose dependent (Fantozzi et al 1986). Silymarin has been shown to exert protective effects in the early phase of asthma, most likely due to its influence on histamine release (Breschi et al 2002).

Antifibrotic

Silymarin reduces markers for collagen accumulation in the liver and exerts antifibrotic activity, according to an animal model of liver fibrosis (Boigk et al 1997).

Antitumour effects

In a variety of in vitro and in vivo research, silymarin and silybin have demonstrated both cancer-preventive and anticancer activities, although the antitumour activity is less than for some other herbals such as Wild Yam, echinacea, cayenne, and astragalus (Mazzio & Soliman 2008). In addition, a research shows antimetastatic activity in animal studies (Raina et al 2008, Ramasamy & Agarwal 2008).

Strong anticancer effects have been identified in human skin, cervical, prostate, bladder, colon, breast carcinoma, hepatocellular carcinoma, laryngeal squamous carcinoma cells (Bang et al 2008, Hogan et al 2007, Post-White et al 2007, Varghese et al 2005, Vinh et al 2002, Zi & Agarwal 1999, Zi et al 1998a, 1998b, Zhao et al 1999, Zhu et al 2001). One study reported that 0.05–0.1% of silybin in the diet did not show any effects on pulmonary adenoma formation and growth in mice (Yan et al 2005), but inhibited lung tumour angiogenesis in mice (Singh et al 2006).

Two studies involving the use of topical silymarin in hairless mice before chemical carcinogenesis and photocarcinogenesis have shown a protective effect that resulted in a statistically significant decrease in tumour incidence, tumour multiplicity and tumour volume per mouse in the treated groups (Wright et al 2006). Furthermore, this chemopreventive effect was found to be dose dependent in one of the studies, in which the topical application ranged from 3 to 12 mg per mouse, with the 12-mg application conferring the most protection.

It appears that several mechanisms are responsible for the chemopreventive and anticancer effects, besides an antioxidant effect (Agarwal et al 2006, Gazak et al 2007). In vivo research has demonstrated chemopreventive effects for silymarin, by inhibiting endogenous tumour promoter TNF-alpha (Zi et al 1997). Anti-angiogenic activity has also been observed, and is likely to be involved (Jiang et al 2000). For example, in a mouse prostate adenocarcinoma model, silybin showed antiproliferative effects and inhibited angiogenesis (Raina et al 2008). In human colon cancer cells, milk thistle displayed antiproliferative effects through cell-cycle arrest via inhibition of cyclin-dependent kinase promoter activity (Hogan et al 2007). Investigating prostate carcinoma cells, researchers found that p21 and p27 induction played a role in silybin-mediated cell-cycle arrest (Roy et al 2007).

Research also shows that silymarin inhibits the increase in mast-cell density in a developing neoplasm and downregulates the expression of matrix metalloproteinases 2 and 9, which are involved in invasion and angiogenesis and therefore required for metastasising (Lee et al 2007, Ramakrishnan et al 2008). Lee et al found that silybin suppresses PMA-induced MMP-9 expression by blocking the AP-1 activation via MAPK signalling pathways in MCF-7 human breast carcinoma cells (Lee et al 2007). In addition to a decreased expression of matrix metalloproteinases, mesenchymal markers snail-1, and fibronectin in the prostatic tissue and retention of epithelial characteristics may also be associated with a decrease of metastasis (Raina et al 2008). Silybin was found to exert a dose- and time-dependent inhibitory effect on the viability, motility and adhesion of highly metastatic prostate cancer cells (Mokhtari et al 2008).

In vitro studies have shown that silymarin possesses high cancer-preventive effects in different mouse skin carcinogenesis models. Silymarin provides substantial protection against different stages of UVB-induced carcinogenesis, via its strong antioxidant properties (Katiyar et al 1997, Svobodova et al 2007) and a selective action on NF-kappaB activation (Saliou et al 1999). Topical application of silymarin provided significant protection against different stages of UVB-induced skin carcinogenesis in mouse skin tumourigenesis models (Ahmad et al 1998, Lahiri-Chatterjee et al 1999). Investigations have demonstrated that silymarin inhibited UV-induced oxidative stress through targeting infiltrating the CD11b+ cell type in the skin (Katiyar et al 2008). An earlier study found silybin has a protective effect against UV radiation in human keratinocytes by inactivation of caspase-8 after direct downregulation of Fas-associating protein with death domain (Hoh et al 2006). Similarly, in human malignant melanoma cells silymarin exaggerated the apoptotic effect of anti-Fas agonistic antibody CH11 (Li et al 2007). Topical and systemic silymarin caused an upregulation of tumour suppressor genes p53 and p21CIP1 (Saller et al 2007). It has also been shown that systematic and topical application of silymarin was effective against burn-induced oxidative damage and morphological alterations in rat skin (Toklu et al 2007).

Contradictory results exist for the effects of milk thistle on breast cancer cells. In rats, silymarin modestly increased the number of mammary tumours (Malewicz et al 2006). Also, treatment of MCF-7 cells with serum-achievable concentrations of silymarin in the rodent models stimulated their growth, partially through an oestrogen-like activity (Malewicz et al 2006). In contrast in tumoural mammary glands in transgenic mice, tumour growth was inhibited by silymarin (Provinciali et al 2007). However, in a multiple mammary adenocarcinoma mouse model, silybin or silipide did not promote or interfere with tumour development (Verschoyle et al 2008).

OTHER ACTIONS

Cholesterol lowering

Cholesterol reduction has been demonstrated for silymarin in two studies of rats fed a high-cholesterol diet (Krecman et al 1998, Sobolova et al 2006). Although the mechanism of action is unknown, it has been suggested that inhibition of HMG-CoA reductase (Skottova & Krecman 1998a) and inhibition of cholesterol absorption from dietary sources (Sobolova et al 2006) are involved.

Considering that the herb also contains phytosterols, these too may play a role in cholesterol reduction.

Neuroprotective

Silymarin demonstrated neuroprotective activity according to preliminary research. A study by Wang et al (2002) demonstrated that silymarin could effectively protect dopaminergic neurons against lipopolysaccharide-induced neurotoxicity by inhibiting activation of the microglia that represent resident macrophage-like population of brain cells acting in host defence and tissue repair in the CNS. Silymarin induced an increase of reduced glutathione and ascorbic acid levels and superoxide

dismutase activity in the brain of treated rats (200 mg/kg/day PO) for 3 days, showing a protective effect on antioxidant defence systems.

Pharmacokinetics

Silybin undergoes fast absorption and elimination and has dose-related pharmacokinetics in the dose ranges of 10–50 mg/kg. The authors suggest active hepatobilliary excretion partially inhibited by P-gp (Wu et al 2008). Silybin administration in rats gave greater bile levels of unconjugated silybin and total silybin than in plasma and the oral bioavailability of silybin in rats was estimated to be 0.73% (Wu et al 2007). Silybin can be absorbed in the whole intestine. The uptake of silybin was similar at 190 and 300 microgram/mL (Luan & Zhao 2006).

Following oral administration, silymarin is quickly metabolised. It undergoes phase I and phase II metabolism, especially phase II conjugation reactions, forming glucuronides detectable in human plasma. It undergoes multiple conjugation reactions and is primarily excreted into bile and urine (Pradhan & Girish 2006, Venkataramanan et al 2006, Wen et al 2008, Wu et al 2009). Silymarin has limited effect on the pharmacokinetics of several drugs in vivo, as only a few reports of silymarin decreasing the activity of cytochrome P-450 (CYPs) enzymes and reducing P-glycoprotein (P-gp) transport exist.

Effects on CYP450 enzymes

Conflicting results from different studies make it difficult to determine what effect silymarin has on CYP450 enzymes. Early in vitro studies showed some evidence of CYP3A4 inhibition and, possibly, inhibition of other CYP enzymes (Venkataramanan et al 2000, Zuber et al 2002). Results published in 2002 suggest that the flavolignans silybin, silydianin and silycristin display a dose-dependent inhibition of CYP3A4, CYP2E1 and CYP2D6 (Zuber et al 2002). An in vitro study confirmed the downregulation of CYP3A4 expression by silybin (Budzinski et al 2007).

Three other in vitro studies could not confirm inhibitory effects for silymarin on CYP2E1, with one study actually reporting induction activity (Etheridge et al 2007, Kim et al 1997, Miguez et al 1994). Moreover, another study did not confirm the effects reported for CYP2D6, but showed that milk thistle extract can inhibit CYP2C8 at 10 μm (Etheridge et al 2007).

However, it seems that reported in vitro effects have no clinical relevance in vivo. For example, in 2003, a crossover study of healthy volunteers found that silymarin (160 mg three times daily) had no apparent effect on indinavir plasma concentrations, suggesting no significant effect on CYP3A4 in humans (DiCenzo et al 2003). A subsequent clinical study found no evidence of an interaction between St Mary's thistle and indinavir when administered in commonly used therapeutic doses (DiCenzo et al 2003). Three further clinical studies found milk thistle extract had no significant effect on the pharmacokinetics of CYP3A4 substrates (irinotecan, midazolam, nifedipine).

One study of six cancer patients tested the use of milk thistle (400 mg daily) for 4 days and 12 days, finding no effect on irinotecan clearance and extent of glucuronidation (van Erp et al 2005). Similarly, in a study with healthy volunteers receiving 900 mg of standardised milk thistle extract for 14 days, no effects on the pharmacokinetics of midazolam were observed (Gurley et al 2006a, 2006b). In another human study, silymarin had no significant effect on the metabolism of orally administered nifedipine, but a possible decrease in the absorption rate of nifedipine was noted (Fuhr et al 2007).

Similarly, clinical studies have found no significant effects for milk thistle extract on CYP2D6 (Gurley et al 2008) or CYP2C9 for silmarin (210 mg/day) taken over 28 days (Leber & Knauff 1976).

Effects on P-glycoprotein

An in vitro study identified that silymarin inhibited P-glycoprotein (P-gp) ATPase activity in such a way as to suggest direct interaction with P-gp substrate binding (Zhang & Morris 2003). However, Gurley et al concluded that milk thistle is not a potent P-gp modulator, following their study where milk thistle extracts did not show any effect on digoxin pharmacokinetics in comparison to rifampin and clarithromycin (Gurley et al 2006a, 2006b).

Effects on UDP glucuronosyltransferase

No in vitro effects on UDP glucuronosyltransferase isoform 1A1 were reported (van Erp et al 2005).

CLINICAL USE

Dyspepsia

Although St Mary's thistle has been most commonly investigated for its effects as a hepatoprotective agent, it is commonly used to treat dyspeptic complaints, such as loss of appetite, poor digestion and upper gastrointestinal discomfort. Animal studies have identified a dose-dependent increase in bile flow and bile salt secretion for silymarin, achieved by stimulating the synthesis of bile salts (Crocenzi et al 2000). Silymarin has been found to impact on bile salt synthesis, bile secretion, biotransformation of cholestatic compounds and changes in transported expression and activity (Crocenzi and Roma, 2006).

Commission E approves the use of crude milk thistle preparations for dyspeptic complaints (Blumenthal et al 2000).

Toxic liver damage

Mushroom poisoning (*Amanita phalloides*)

One of the best-documented uses of milk thistle is in the treatment of poisoning by the mushroom *Amanita phalloides* (death cap). Nausea, vomiting, abdominal cramps and severe diarrhoea usually occur 8–12 h after ingestion, with extensive hepatic necrosis occurring 1–2 days later. A mortality rate of 20–30% has been observed but can be as high as 50% in children under 10 years of age (Floersheim et al 1982). Several clinical studies have shown silybin (20–50 mg/kg/day IV) to protect against hepatotoxicity when administered within 48 h.

One report of pooled data from 452 case reports of *A. phalloides* poisoning showed a highly significant difference in mortality in favour of silybin (Saller et al 2001).

Environmental toxins and drugs

In animals, milk thistle reduces acute liver injury caused by paracetamol (Ali et al 2001, Muriel et al 1992), carbon tetrachloride (Favari & Perez-Alvarez 1997, Letteron et al 1990), radiation (Hakova & Misurova 1996, Kropacova et al 1998), iron overload (Masini et al 2000, Pietrangelo et al 1995), phenylhydrazine (Valenzuela & Guerra 1985) and D-galactosamine (Tyutyulkova et al 1981, 1983).

One randomised, double-blind study involving 222 patients showed that silymarin improves the tolerability of tacrine without altering the drug's cognitive effects (Allain et al 1999). Two other clinical trials have documented the effectiveness of silymarin in improving or preventing hepatotoxicity from chronic administration of phenothiazines or butyrophenone (Anon 1989).

Hepatocyte repair

The effects of a commercial silymarin product (Legalon 120 mg three times daily) on liver function tests and liver histology were studied in 36 patients with chronic alcoholic liver disease in a 6-month, double-blind clinical trial (Feher et al 1989). Treatment not only produced significant improvements in liver function test results, but also positive effects on histology, while these parameters remained unchanged in the placebo group. Salmi and Sarna (1982) found similar results in a randomised controlled trial (RCT) of 106 patients with liver disease. After just 4 weeks' treatment, histological changes began to normalise significantly more often in the treated group than in controls.

A review concluded that the clinical evidence for a therapeutic effect in toxic liver disease is scarce, but that it is reasonable to employ silymarin as adjunct therapy in the treatment of *Amanita phalloides* poisoning (Saller et al 2008). Commission E approves the use of standardised St Mary's thistle extracts (70–80% silymarin content) for toxic liver damage (Blumenthal et al 2000).

Supportive treatment in chronic liver diseases

Numerous clinical trials have been conducted with St Mary's thistle preparations in various chronic liver diseases. The most studied treatments are Legalon (Madaus Corporation, Cologne, Germany) and Silipide (Inverni Della Beffa Research and Development Laboratories, Milan, Italy), designed to improve oral absorption of silymarin.

A 1998 clinical review of St Mary's thistle concluded that it may be effective in improving the clinical courses of both acute and chronic viral, drug-induced, toxin-induced and alcoholic hepatitis (Flora et al 1998). A systematic review of efficacy for St Mary's thistle in chronic liver diseases stated that data are still too limited to detect a substantial benefit on mortality or recommend the herb in liver disease (Jacobs et al 2002).

> ***Clinical note — Hepatic fibrosis***
> Hepatic fibrosis is a pathological wound-healing process that occurs when the liver is injured chronically, such as in chronic alcohol abuse. The oxidative metabolite of ethanol, acetaldehyde, often in conjunction with viral or metabolic liver disease, is implicated as the major cause for liver fibrogenesis, which ultimately leads to cirrhosis (Schuppan et al 1995). Antifibrotic agents, which interrupt the continuous process of wound healing in the liver, are being investigated as strategies to prevent or reverse liver cirrhosis.

Twelve clinical studies were located in which researchers have attempted to clarify the role of St Mary's thistle in the treatment of various liver diseases (Angulo et al 2000, Benda et al 1980, Buzzelli et al 1993, Ferenci et al 1989, Loguercio et al 2007, Lucena et al 2002, Magliulo et al 1978, Par et al 2000, Pares et al 1998, Salmi & Sarna 1982, Trinchet et al 1989, Velussi et al 1997). Much of the research focuses on the different forms of hepatitis and alcoholic liver cirrhosis with doses ranging from 100 to 300 mg three times daily, usually given in a standardised extract of 70–80% silymarin. Overall, results have been mixed, with nine trials showing generally positive results and three negative, suggesting that milk thistle is effective in only some forms of liver disease.

Alcoholic liver disease

A 2005 Cochrane review of 13 randomised clinical trials and a 2007 Cochrane review of 18 randomised clinical trials assessed milk thistle in 915 and 1088 patients, respectively, looking at its effect in alcoholic and/or hepatitis B or C virus liver diseases (Rambaldi et al 2007, 2005). The authors stated in both reviews that the methodological quality of the trials was low and that milk thistle versus placebo or no intervention had no significant effect on complications of liver disease or liver histology, and that milk thistle was not associated with a significantly increased risk of adverse events. In comparison to the 2005 review, which concluded that liver-related mortality was significantly reduced by milk thistle in patients with alcoholic liver disease, the 2007 review found that liver-related mortality was significantly reduced by milk thistle in all trials, but not in high-quality trials (Rambaldi et al 2007, 2005). Another review supports this view (Bergheim et al 2005).

Acute viral hepatitis

Several studies have investigated the use of milk thistle in this disease, reporting beneficial effects on serological outcomes (Bode et al 1977, Magliulo et al 1978, Tkacz & Dworniak 1983). However, several studies were not clearly blinded and further research is required to determine whether St Mary's thistle can provide significant benefits in this population.

Hepatitis C infection

A 2003 systematic review of medicinal herbs for HCV infection concluded that compared with placebo, none of the herbs showed effects on HCV RNA or liver enzyme, except for the constituent silybin, which showed a significant reduction of serum AST and gamma-glutamyltranspeptidase levels in one trial (Liu et al 2003). In a 4-week randomised, controlled clinical trial (n = 34) using 160 mg of milk thistle three times a day, AST, ALT and viral load values decreased from baseline levels after 4 weeks although the effect was not significant. In comparison, values for ALT and viral load showed a significant increase in the control group over the same period. When treatment and control groups were then compared, a significant difference was observed for ALT and AST, but not for viral load (Torres et al 2004). Similarly, a 2005 review concluded that silymarin decreases serum AST and ALT levels, but does not seem to affect viral load or liver histology (Mayer et al 2005). A newer randomised, double-blind, placebo-controlled, crossover study (n = 24) where subjects received 12 weeks treatment with 600 or 1200 mg milk thistle daily, viral load, ALT levels and quality of life scores (short-form (SF)-36) were not significantly different to placebo (Gordon et al 2006). As part of the hepatitis C Antiviral Long-Term Treatment Against Cirrhosis (HALT-C) trial (n = 1145 participants), involving people with advanced chronic hepatitis C, non-responders to prior antiviral therapy continued taking pegylated interferon treatment with the addition of oral silymarin therapy; however, no changes to ALT and viral load were observed with adjunctive herbal treatment. Silymarin therapy did significantly lower liver-related symptoms and improved QOL parameters such as fatigue, nausea, liver pain, anorexia, muscle and joint pain, as well as general health (Seeff et al 2008). Intravenously administered silymarin produced a substantial antiviral effect against HCV in pedigreed non-responders to full-dose pegylated interferon/ribavirin and was well tolerated (Ferenci et al 2008).

Surprisingly, a review found no evidence for a beneficial effect of silymarin on the progression of viral hepatitis, especially hepatitis C (Saller et al 2008).

Commission E approves the use of standardised St Mary's thistle extracts (70–80% silymarin content) as supportive treatment in chronic inflammatory liver disease and hepatic cirrhosis (Blumenthal et al 2000). A review concluded that silymarin 'is reasonable' to be employed as an adjunct therapy for alcoholic and grade Child 'A' liver cirrhosis (Saller et al 2008).

Diabetes

Silymarin has also been investigated in diabetic patients with cirrhosis. Velussi et al (1997) investigated whether long-term treatment with silymarin is effective in reducing lipoperoxidation and insulin resistance in diabetic patients with cirrhosis. The 6-month open trial found that silymarin treatment had several benefits. After the first month's treatment, fasting glucose levels showed a progressive and significant decline that, interestingly, did not lead to an increase in the frequency of hypoglycaemic episodes. Other observations revealed decreased glucosuria and levels of glycosylated haemoglobin also decreased significantly, indicating an overall improvement in glucose control. The dose used was 600 mg/day silymarin.

OTHER USES

Traditionally, the seeds have been used to treat jaundice, hepatitis, haemorrhoids and psoriasis, as a tonic for nursing mothers, and as a general 'liver cleansing' agent.

Hypercholesterolaemia

In clinical practice, it is not unusual to find treatment with St Mary's thistle at the higher end of the dose range results in cholesterol lowering effects. Several in vivo studies confirm that St Mary's thistle increases LDL cholesterol clearance and raises HDL cholesterol levels; however, only one clinical trial is available to determine whether the effect is clinically significant (Krecman et al 1998, Skottova & Krecman 1998b, Somogyi et al 1989). An open trial involving 14 subjects with type 2 hyperlipidaemia found that treatment with silymarin (420 mg/day) slightly reduced total cholesterol and HDL cholesterol levels (Somogyi et al 1989).

Cancer prevention and treatment

In vivo research suggests that silymarin and/or its major active constituent silibinin could be an effective agent for prevention and/or supportive treatment of human skin cancer (Singh et al 2002, Zhao et al 2000). Topical application of silymarin provided significant protection against different stages of UVB-induced skin carcinogenesis in mouse skin tumourigenesis models (Ahmad et al 1998, Lahiri-Chatterjee et al 1999).

Chemotherapy support

The role of St Mary's thistle as adjunctive therapy in a range of cancer treatments has received much interest in the past few years. Silybin appears to have nephroprotective activity effective against cisplatin and vincristine toxicity in vitro (Sonnenbichler et al 1999). Protection against cisplatin nephrotoxicity has been confirmed in vivo by Gaedeke et al (1996), who showed that the adverse effects of cisplatin on creatinine clearance and proteinuria were totally prevented by silybin pretreatment. Bokemeyer et al (1996) confirmed the nephroprotection afforded by silybin in a rat animal model and observed that it did not alter the clinical efficacy of cisplatin. According to an in vivo study by Karimi et al (2005), both silymarin and St Mary's thistle extract are also effective when given as pretreatment before cisplatin.

In vitro and in vivo research has further shown that a combination of silybin with cisplatin produces a dose-dependent and statistically significant increase of drug activity, resulting in a potentiation of antitumour activity (Giacomelli et al 2002, Scambia et al 1996).

Clinical note — Cisplatin
Cisplatin is one of the most active cytotoxic agents in the treatment of testicular cancer, but its clinical use is associated with side effects, such as severe nausea, ototoxicity, neurotoxicity and nephrotoxicity (Giacomelli et al 2002). It is also used in the treatment of head and neck, gastrointestinal, cervical, lung and bladder cancer.

Diabetes
A 4-month randomised, double-blind, placebo-controlled trial in 51 type 2 diabetes patients receiving silymarin (200 mg three times daily) as an adjunct treatment to their conventional therapy showed a significant decrease in HbA_{1c}, fasting blood glucose, total cholesterol, LDL and triglyceride levels compared with placebo as well as with values at the beginning of the study in each group (Huseini et al 2006).

DOSAGE RANGE
- The average daily recommended dose is 12–15 g (practitioners have used doses as high as 18 g/day) of milk thistle seed, usually in divided doses (equivalent to 200–400 mg silymarin) (WHO 2003).
- Liquid extract (1:1): 4–9 mL/day (Mills & Bone 2000).
- Liquid extract (1:2): 30–60 mL/week.
- Silybin-phytosome: 13 g daily (Flaig et al 2007)

TOXICITY

Extremely low
Toxicity studies in rats and mice have shown that silymarin, even at daily doses as high as 2500–5000 mg/kg, produced no adverse toxic effects (Madaus 1989). In a 12-month study in rats and dogs given up to 2500 mg/day, no signs of toxicity were seen. Milk thistle products with a standardised content of silymarin (70–80%) were found to be safe for up to 41 months of usage (Francine 2005).

ADVERSE REACTIONS
Milk thistle is considered safe and well tolerated when taken within the recommended dose range (Post-White et al 2007). A review of studies involving more than 7000 participants identified three cases of serious adverse reactions (two anaphylaxis and one gastroenteritis symptoms) (Jacobs et al 2002). In one clinical trial, patients with colorectal adenocarcinoma who received silipide (silybin with phosphatidylcholine) at dosages of 360, 720 or 1440 mg daily for 7 days found the administration of silipide to be safe (Hoh et al 2006). Another clinical trial (n = 13) reported hyperbilirubinaemia in 9/13 patients and increased ALT in 1/13 patients using silybin-phytosome (Flaig et al 2007), whereas all other trials reported only rare adverse events (Gordon et al 2006, Rainone 2005, Torres et al 2004), mostly gastrointestinal symptoms, even for intravenously administered silymarin (Ferenci et al 2008). Reviews concluded that silymarin has an excellent safety profile (Dryden et al 2006, Rainone 2005, Sagar 2007).

Overall, adverse effect frequency was the same as for placebo and had a low frequency, ranging from 2% to 10% in controlled trials. In practice, loose bowels have been reported, although the reaction is considered rare.

SIGNIFICANT INTERACTIONS
Although some in vitro evidence indicates that effects on cytochrome P-450 (CYPs) enzymes and P-glycoprotein (P-gp) transport exist, several in vivo studies report limited or no effects on the pharmacokinetics of several drugs (Wu et al 2009). Importantly, clinical trials indicate no significant changes in the pharmacokinetic profiles of several CYP3A4 substrates (Fuhr et al 2007, Gurley et al 2006a, 2006b, van Erp et al 2005), P-glycoprotein (Gurley et al 2006a, 2006b), CYP2D6 (Gurley et al 2008) or CYP2C9 (Leber & Knauff 1976).

Cisplatin
Preliminary research has shown this combination may reduce toxic effects, yet enhance antitumour activity — adjunctive use may be beneficial when used under professional supervision.

Doxorubicin
Silymarin reduces cardiotoxicity and possibly chemosensitises resistant cells to anthracyclines — adjunctive use may be beneficial when used under professional supervision.

Hepatotoxic substances
General hepatoprotective effects reported for silymarin — adjunctive use may be beneficial when used under professional supervision.

CONTRAINDICATIONS AND PRECAUTIONS
Contraindicated in people with known allergy to the Asteraceae (Compositae) family of plants. One case of exacerbation of haemochromatosis due to ingestion of milk thistle has been reported (Whittington 2007); however, the association between herbal intake and outcome reported is unlikely (Kidd 2008).

PREGNANCY USE
Insufficient reliable information is available to determine safety in pregnancy.

PATIENTS' FAQs
What will this herb do for me?
St Mary's thistle may improve digestion, particularly of fatty foods, and afford protection against the toxic effects of a number of drugs and environmental poisons. It is also used as supportive treatment in chronic liver diseases and high-cholesterol states.
When will it start to work?
This varies, depending on the indication.
Are there any safety issues?
St Mary's thistle is considered a very safe and well-tolerated herb.

ADDITIONAL READING
For the interested reader, a comprehensive review exists summarising most clinical trials on the safety and efficacy of milk thistle (Tamayo & Diamond

2007). Two other comprehensive reviews summarise milk thistle's mechanism of action (Comelli et al 2007) and clinical application in oncology (Greenlee et al 2007a, 2007b).

PRACTICE POINTS/PATIENT COUNSELLING

- St Mary's thistle has hepatoprotective activity and has been shown to reduce the hepatotoxic effects of a variety of environmental toxins and medicines, such as paracetamol, erythromycin, carbon tetrachloride and death cap mushrooms.
- It has direct and indirect antioxidant activities, accelerates the regeneration of hepatocytes after liver damage, has significant gastroprotective and nephroprotective activities, anti-inflammatory and antihistamine activities, according to in vitro and animal studies.
- Numerous clinical studies have investigated its effects in a variety of liver diseases, although reviews still conclude that current data are insufficient to routinely recommend the herb in chronic liver diseases.
- In clinical practice, it is used to treat dyspepsia, toxic liver damage, as supportive therapy in chronic liver diseases and hypercholesterolaemia.
- Preliminary evidence suggests a possible role as adjunctive therapy with cisplatin and as a skin cancer preventative agent when applied topically.

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Saw palmetto

HISTORICAL NOTE Saw palmetto was used traditionally as a treatment for urogenital irritations, impotence and male infertility, among other conditions, and was described by the American Eclectic physicians as the 'old man's friend'. Between 1906 and 1917 saw palmetto was listed in the US Pharmacopoeia and between 1926 and 1950 it was in the National Formulary as a treatment for urogenital ailments; however, it fell out of favour for several decades as pharmaceutical medicines came to the forefront of mainstream medicine. Not so in Europe where, in the 1960s, French researchers began to chemically analyse the saw palmetto berry, and a breakthrough lipophilic preparation was eventually developed and subjected to countless clinical trials.

COMMON NAME
Serenoa or saw palmetto

OTHER NAMES
American dwarf palm tree, cabbage palm, dwarf palmetto, fan palm, sabal fructus, sabal, serenoa

BOTANICAL NAME/FAMILY
Sabal serrulata, Serenoa repens (family Arecaceae or Palmaceae)

PLANT PART USED
Dried ripe fruit

CHEMICAL COMPONENTS
An ethanol extract of the berry contains free fatty acids rich in shorter chain-length fatty acids, such as capric, caprylic, lauric and myristic acids (Nemecz 2003). Palmitic, stearic, oleic, linoleic and linolenic acids are also present in the extract. There are also lesser amounts of phytosterols (such as beta-sitosterol, stigmasterol, ampesterol and cycloartenol), aliphatic alcohols and polyprenic compounds. The lipophilic extract is used medicinally.

MAIN ACTIONS
The mechanism of action is not fully elucidated; however, it appears that several mechanisms are at work.

Inhibition of 5-alpha reductase
In different cell systems, the lipid-sterolic extract acts as a non-competitive inhibitor of both type 1 and type 2 5-alpha reductase activity, thereby preventing the conversion of testosterone to dihydrotestosterone (Bayne et al 2000, Raynaud et al 2002, Sultan et al 1984). However, it is currently unclear whether the effect is apparent in humans, as contradictory evidence exists. Raynaud et al (2002) explained that the discrepancies found by different authors were due to different experimental conditions and selectivity for fatty acids, as only specific aliphatic unsaturated fatty acids have been shown to inhibit 5-alpha reductase activity.

One study that analysed and compared benign prostatic hyperplasia (BPH) samples taken from both untreated and treated subjects (320 mg saw palmetto extract taken for 3 months) found that local levels of testosterone were raised, whereas dihydrotestosterone levels were reduced, suggestive of local 5-alpha reductase inhibition (Di Silverio et al 1998). An earlier, short-term study found that a dose of 160 mg of a liposterolic extract (Permixon) produced no changes to serum dihydrotestosterone levels, whereas finasteride 5 mg induced a significant reduction (Strauch et al 1994). Since prostate levels were untested in this study, it is not known whether a local effect occurred, even though serum levels remained unchanged.

Unlike other 5-alpha reductase inhibitors, there is no interference with the cell's capacity to secrete prostate-specific antigens because it does not affect the transcription of the gene for prostate-specific antigen (PSA), as demonstrated both in vitro and in vivo (Maccagnano et al 2006). Although having an obvious clinical advantage with regard to PSA screening for prostate cancer, this also suggests that 5-alpha reductase inhibition is not a major activity.

Inhibits binding of dihydrotestosterone and testosterone to androgen receptors
Saw palmetto reduces receptor binding of dihydrotestosterone and testosterone by an average of 41%, as tested in 11 different tissue specimens from BPH patients (el Sheikh et al 1988). In 2003, results from two animal studies showed that saw palmetto (whole berry and extract) influenced prostatic hyperplasia via effects on androgen metabolism (Talpur et al 2003).

Inhibits prolactin
In vivo research has identified not only an inhibitory effect on androgens, but also on the trophic effect of prolactin in the rat prostate (Van Coppenolle et al 2000). The inhibitory effect on prolactin activity appears to be due to inhibition of several steps in prolactin receptor signal transduction, according to one animal model (Vacher et al 1995).

Anti-inflammatory
Saw palmetto is a dual inhibitor of the COX and 5-lipoxygenase pathways, according to in vitro research (Breu et al 1992, Paubert-Braquet et al 1997). More recently, decreased expression of COX-2 has been identified, providing a further explanation for the observed anti-inflammatory activity (Goldmann et al 2001).

Antispasmodic
Both the lipid and saponifiable fractions have demonstrated antispasmodic activity in several in vitro studies (WHO 2003).

Cytochromes

Saw palmetto failed to have a significant effect on CYP3A4 or CYP2D6 when tested in healthy individuals (Markowitz et al 2003).

Antiproliferative effects

In recent years, there has been interest in determining whether saw palmetto may have a role in prostate cancer, as an inhibitory activity has been observed in several test tube studies for prostatic cancer cell lines (Goldmann et al 2001, Ishii et al 2001).

OTHER ACTIONS

Although alpha-1 adrenoreceptor activity has been reported in vitro, a clinical study found no evidence of this activity (Goepel et al 1999, 2001). Saw palmetto does not affect platelet function in vivo (Beckert et al 2007).

Traditionally, saw palmetto is believed to act as a mild diuretic, urinary antiseptic and expectorant.

CLINICAL USE

The most studied saw palmetto preparation is a commercial product known as Permixon (Pierre Fabre Médicament, Castres, France), which is a liposterolic extract consisting of 80% free (e.g. 94 g/100 g extract) and 7% esterified fatty acids, as well as small amounts of sterols (beta-sitosterol, campesterol, stigmasterol, cycloartenol), and a minimum percentage of polyprenic compounds, arabinose, glucose, galactose, uronic acid and flavonoids.

BPH

Saw palmetto extracts are extremely popular in Europe where herbal preparations represent approximately one-third of total sales of all therapeutic agents sold for the treatment of BPH (Levin & Das 2000). In Germany, for instance, more than 30 different preparations containing saw palmetto are on the market. By far, most intensively studied product of this group is a n-hexane-liposterol-extract (Permixon® by Pierre Fabre Medicament, Boulogne, France), which is very popular in France and Italy. It is a complex mixture of free fatty acids and their esters, phytosterols, aliphatic alcohols and various polyprenic compounds (Madersbacher 2007).

Substantial evidence suggests that saw palmetto is an effective treatment for stages 1 and 2 of BPH. A 2002 Cochrane review assessing the results from 21 randomised trials involving 3139 men concluded that saw palmetto improves urinary scores, symptoms and urinary flow measures compared with placebo, with effects on symptoms scores and peak urine flow similar to the pharmaceutical drug finasteride (Wilt et al 2002). Additionally, its use is associated with fewer adverse effects compared with finasteride and, typically, symptomatic relief is reported more quickly.

In 2004, an updated meta-analysis of 14 randomised studies and three open-label studies was published (Boyle et al 2004). The analysis used data from 4280 patients derived from clinical studies that had used Permixon. Three randomised trials had a study period of 6 months or longer. Peak urinary flow rate and nocturia were the two common endpoints. Active treatment was associated with a mean reduction in the International Prostate Symptom Score (IPSS) of 4.78 (0.41). A significant improvement in peak flow rate and reduction in nocturia was also reported.

Since then, a double-blind study of 1 year of continuous treatment with saw palmetto extract (160 mg twice daily containing 92.1% total fatty acids) failed to produce significant differences compared with placebo for the American Urological Association Symptom Index, maximal urinary flow rate, prostate size, residual volume after voiding, quality of life or serum PSA levels (Bent et al 2006). It is unclear why this trial is contradictory to the general body of evidence that supports the use of saw palmetto in BPH. Bent et al suggest that previous studies had inadequate blinding; however, this seems unlikely for all studies. Another possible explanation relates to the differences in herbal extracts tested in different studies. Additionally, saw palmetto is most often used in cases of mild BPH, whereas this study included subjects with moderate-to-severe BPH, which may have contributed to the results observed; however, this is speculative.

In 2007, results of the European TRIUMPH study were published which provided support for the effectiveness of saw palmetto under real-world conditions, although it does not have benefits in everyone (Hutchison et al 2007). The study recorded treatment and outcomes of 2351 newly presenting men with lower urinary tract symptoms (LUTS) suggestive of BPH in six European countries over a 1-year follow-up period. At each visit, the clinician recorded the treatment, co-morbidities, complications and drugs prescribed, and the patient completed an IPSS questionnaire. The results were analysed using change in IPSS as the primary outcome measure. The efficacy of the three classes of drug (alpha-blockers, 5-alpha reductase and phytotherapy) was investigated by randomly matching each patient receiving only one class of drug over the study period to a watch-and-wait case on age at diagnosis (±2 years) and initial IPSS (±2 IPSS points). Based on this evaluation, authors concluded that significant improvements were seen in 43% of patients taking phytotherapy with *Serenoa repens* or *Pygeum africanum*. Saw palmetto produced a significant improvement in symptoms compared to untreated men ($P = 0.0003$). The best effects were seen with tamsulosin, which was also the most prescribed drug.

Positive results were obtained by Shi et al (2008) where treatment with Prostataplex™ (2 caps/day) significantly increased maximum urinary flow rate compared to placebo under double-blind test conditions. The 12-week study of 92 Chinese men (49–75 years) with lower urinary tract symptoms associated with BPH also found that active treatment significantly reduced relative urinary resistance. Interestingly, no significant difference in mean prostate volume or IPSS was found between the two groups; however, 18 of 46 patients (39.1%) in the treatment group showed an

IPSS improvement (decrease of three or greater) after intervention, whereas only 1 of 46 (2.2%) in the control group showed an IPPS improvement ($P < 0.001$).

Comparisons with alpha-adrenoreceptor antagonists

Although several comparative trials have been undertaken with finasteride, only a few have compared it with alpha-adrenoreceptor antagonist drugs, which are also commonly used in BPH (Adriazola et al 1992, Debruyne et al 2002). A large, randomised, double-blind study involving 811 men with symptomatic BPH, who were recruited from 11 European countries, showed that Permixon 320 mg/day produced similar results to tamsulosin 0.4 mg/day (Omnic) (Debruyne et al 2002). More specifically, both treatments reduced the IPSS by an average of 4.4 in 80% of subjects. Those patients with the most severe disease experienced the greatest improvement in IPSS total score, with mean changes greater in the Permixon group than in the tamsulosin group (–8.0 and –6.8, respectively). With regard to safety, both treatments were considered well tolerated; however, ejaculation disorders were significantly more frequent with tamsulosin (4.2%) than with Permixon (0.6%). Although these results are promising, this study has been criticised for not including a placebo group as a comparator.

In a short 3-week study, Grasso et al (1995) compared the effects of alfuzosin (7.5 mg/day) with saw palmetto (320 mg/day) in 63 BPH subjects under double-blind test conditions. Both treatments were found to be equally effective with regard to improving irritative score; with maximum and mean urine flow; however, alfuzosin was shown to more rapidly reduce symptoms of obstruction. Considering most studies have shown that 4–8 weeks' treatment with the herb is required to produce maximal effects, the effect seen at 3 weeks is encouraging.

An earlier study compared the effects of prazosin with saw palmetto in 45 patients with BPH over a 12-week period (Adriazola et al 1992). This study found that although both treatments reduced symptoms, prazosin was slightly more effective.

Changes to prostate size

It is still open to speculation as to whether saw palmetto affects prostate size, because studies have produced contradictory results (Aliaev et al 2002, Bent et al 2006, Pytel et al 2002). One open study of 155 men tested the effectiveness and tolerability of Permixon (160 mg twice daily) over 2 years (Pytel et al 2002), and not only detected a significant improvement in the IPSS and quality of life (QOL) marker, but also a decrease in prostate size and significant improvement in sexual function after the first year of treatment.

A longer 5-year study using Permixon in 26 subjects with BPH showed that a total daily dose of 320 mg twice daily also significantly reduced disease symptoms and improved QOL, while reducing prostate size by an average of 30% (Aliaev et al 2002).

> ***Clinical note — BPH***
> BPH occurs in more than 50% of men over the age of 50 years. It is a slow, progressive enlargement of the fibromuscular and epithelial structures of the prostate gland, which can lead to obstruction of the ureter and urine retention. Symptoms such as frequent and/or painful urination, painful perineal stress and a decrease in urine volume and flow can develop. The condition has four stages, with stage 1 considered mild, stages 2 and 3 considered more severe and often requiring pharmacological treatment, and stage 4 as severe and necessitating surgery.

In 2003, results from two animal studies showed that saw palmetto (whole berry and extract) significantly diminished prostatic hyperplasia (Talpur et al 2003). In contrast, the 2006 study discussed earlier failed to find a significant effect on prostate size (Bent et al 2006).

Commission E approves the use of saw palmetto for stages 1 and 2 of BPH (Blumenthal et al 2000).

Androgenetic alopecia

The idea of using saw palmetto for androgenetic alopecia (AGA) arose from the observation that finasteride appears to have some effect on this condition. One double-blind study has investigated the effects of saw palmetto as a potential therapeutic option, finding a highly positive response in 60% of subjects (Prager et al 2002). A second double-blind study of 48 men and women with AGA noted that mean hair density increased by 17% after 10 weeks of treatment with a topical lotion containing saw palmetto and by 27% after 50 weeks of treatment compared to baseline (Morganti et al as reported in Linde et al 2006, Ulbricht & Basch 2006).

Chronic prostatitis and pelvic pain

Evidence to support the herb's use in prostatitis is scarce. However, in April 2003, positive findings from a preliminary study using Permixon to treat symptoms of chronic prostatitis and chronic pelvic pain syndrome (CP/CPPS) were presented at the annual meeting of the American Urological Association (AUA 2003). The RCT involving 61 patients with category IIIB CP/CPPS found that 75% receiving active treatment experienced at least mild improvement in symptoms, compared with 20% of the control group. Furthermore, 55% of patients receiving Permixon reported moderate or marked improvement, compared with 16% of the control group. In contrast, results from a 2004 prospective, randomised, open-label study failed to find benefits for saw palmetto (325 mg daily) in men diagnosed with category III CP/CPPS (Kaplan et al 2004). After 1 year, the mean total National Institutes of Health Chronic Prostatitis Symptom Index score decreased from 24.7 to 24.6 ($P = 0.41$) and no benefits were seen for QOL or pain with saw palmetto treatment.

OTHER USES

Traditionally, saw palmetto has been used to treat a variety of urogenital conditions, such as impotence, male infertility and also as an aphrodisiac. It has also been used in female hirsutism, although its effectiveness in this condition is unknown.

DOSAGE RANGE

- Liposterolic extract: 320 mg/day in divided doses.
- Dried berry: 2–4 g.
- Liquid extract (1:2): 2–4.5 mL/day.

According to clinical studies

- 160 mg twice daily of liposterolic extract taken long term.

ADVERSE REACTIONS

The herb is generally well tolerated, with only non-specific symptoms reported, such as gastrointestinal upset, constipation, nausea, abdominal pain and diarrhoea. These minor complaints are generally resolved by taking the herb in association with meals (Maccagnano et al 2006).

The 1-year STEP study provided a detailed assessment of the potential toxicity of saw palmetto, including both symptomatic adverse effects, as well as asymptomatic laboratory abnormalities (Avins & Bent 2006). It found no evidence that consumption of saw palmetto extract (160 mg twice daily) over a period of 1 year was associated with any clinically important adverse effects. Relatively few participants suffered serious adverse events, and these were more common in the placebo-allocated participants. Additionally, no statistically significant differences were observed between the saw palmetto and placebo groups in the measured domains of sexual functioning with the exception of the perception-of-sexual-problems domain which showed a small but significantly greater improvement in the placebo group.

SIGNIFICANT INTERACTIONS

No controlled studies are available and theoretical interactions are difficult to predict, due to the poorly understood nature of the herb's mechanism of action.

Finasteride (and other 5-alpha reductase inhibitor agents)

Additive effect theoretically possible — potential beneficial effect, although the clinical significance is unknown.

Androgenic drugs

Theoretically, saw palmetto may reduce effectiveness of therapeutic androgens such as testosterone — observe patient for lack of drug effect.

CONTRAINDICATIONS AND PRECAUTIONS

If symptoms of BPH worsen, blood is detected in the urine, or acute urinary retention occurs, professional reassessment is required.

PREGNANCY USE

Use of saw palmetto during pregnancy is contraindicated due to the herb's hormonal effects. In clinical practice, it is not used in pregnancy.

PRACTICE POINTS/PATIENT COUNSELLING

- Substantial scientific evidence has shown that saw palmetto is an effective treatment for stages 1 and 2 of BPH in cases where the diagnosis of cancer is negative. It is as effective as finasteride and alpha-adrenoreceptor antagonist drugs such as tamsulosin and alfuzosin, although prazosin may be slightly more effective.
- Typically, symptom reduction is experienced within 1–2 months' treatment, which is well tolerated, and associated with fewer side effects than finasteride and tamsulosin.
- The herb does not affect PSA levels; therefore, PSA test results will be unaffected.
- If symptoms worsen, blood is detected in the urine or acute urinary retention occurs, seek professional advice.

PATIENTS' FAQs

What will this herb do for me?

Saw palmetto has been investigated in numerous scientific studies and shown to reduce symptoms of enlarged prostate with few side effects. There is also some early research suggesting that it may be useful in some forms of hair loss and prostatitis.

When will it start to work?

Symptom relief for enlarged prostate is generally experienced within 4–8 weeks.

Are there any safety issues?

Saw palmetto is well tolerated; however, occasionally mild gastrointestinal disturbances, headaches and rhinitis have been reported.

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Schisandra

HISTORICAL NOTE Schisandra has an extensive history of use in Traditional Chinese Medicine (TCM). It has sour and warm qualities and is used to treat spleen and kidney 'deficiency', to restore Qi and also as a treatment for chronic cough, wheezing, diabetes, insomnia and palpitations.

OTHER NAMES
Chinese magnolia vine, gomishi, sheng-mai-san, wuweizi

BOTANICAL NAME/FAMILY
Schisandra chinensis (family Schisandraceae)

PLANT PART USED
Fruit

CHEMICAL COMPONENTS
Dibenzocyclooctene lignans (schisandrin, schisandrins A–C, schizabdrols, schisantherins and gomisin A), essential oil, malic, tartaric, nigranoic and citric acids, resins, pectin, vitamins A, C and E, niacin, beta-carotene, sterols, tannins and several minerals.

MAIN ACTIONS
Studies have been conducted with schisandra and a number of its constituents in isolation, such as schisandrin B and gomisin A. Currently, most evidence is derived from in vitro and animal studies, as it has not been significantly investigated in clinical studies.

Antioxidant
In vitro tests have identified antioxidant activity (Ohsugi et al 1999). More specifically, seven lignans isolated from schisandra have demonstrated stronger antioxidant activity than vitamin E at the same concentrations, with schisanhenol exhibiting the strongest effects (Lu & Liu 1992). An extract of schisandra and the isolated constituent schisandrin B have both demonstrated the ability

to significantly decrease alanine aminotransferase (ALT) and increase glutathione levels in CCL4-damaged liver in vivo (Chiu et al 2002). It appears that several constituents also have indirect antioxidant activity and can increase hepatic and myocardial glutathione levels (Yim & Ko 1999).

Hepatoprotective activity

Decreases hepatotoxic damage

Several in vitro and in vivo studies have identified hepatoprotective effects with schisandra against carbon tetrachloride toxicity (Ip et al 1995, Mak & Ko 1997, Zhu et al 1999, 2000, Chiu et al 2007). Research with schisandrin B suggests that it is the main constituent responsible for these beneficial effects (Ip et al 1995, Mak et al 1996, Pan et al 2002, Chiu et al 2007). Further investigation reveals that schisandrin B increases the efficiency of the hepatic glutathione antioxidant system, thereby inhibiting carbon tetrachloride-induced lipid peroxidation; however, additional mechanisms appear likely (Ip et al 1995). More recently, the whole extract of schisandra fruit was shown to induce glutathione S-transferases in vitro (Choi et al 2008).

Protection against paracetamol-induced liver damage has been demonstrated in two animal models using gomisin A (Yamada et al 1993, Kim et al 2008). In one study, gomisin A inhibited not only the elevation of serum aminotransferase activity and hepatic lipoperoxide content, but also the appearance of histological changes such as degeneration and necrosis of hepatocytes (Yamada et al 1993).

In 2003, protection against paracetamol-induced liver damage and D-galactosamine-induced liver damage was confirmed for a fractionated extract of *S. chinensis* in an experimental model (Nakagiri et al 2003).

Liver regeneration

Two animal studies have demonstrated that oral administration of gomisin A, a lignan isolated from *S. chinensis*, accelerates liver regeneration after partial hepatectomy and hastens recovery of liver function (Kubo et al 1992, Takeda et al 1987). The mechanism for these effects is not fully elucidated; however, gomisin A increases ornithine decarboxylase activity, which is important during the early stages of regeneration and suppresses fibrosis proliferation.

Anti-inflammatory

Schisandrin inhibits NO production, prostaglandin E(2) release, cyclo-oxygenase (COX)-2, nitric oxide synthase (iNOS) and nuclear factor-kappaB in vitro (Guo et al 2008). Animal studies have also identified anti-inflammatory activity for gomisin A, gomisin J and wuweizi C (Yasukawa et al 1992). Several lignans from schisandra, including gomisin N and schisandrol A, have shown potent inhibition of nuclear factor of activated T cells (NFAT) in vitro (Lee et al 2003). Excessive activation of NFAT has a significant role to play in autoimmune disease, but further study is needed to assess schisandra's usefulness in immunopathological disease states.

A water extract of schisandra has demonstrated potent effects in a mast cell line (Kang et al 2006). The extract inhibits TNF-alpha, IL-6 and granulocyte-macrophage colony-stimulating factor (GM-CSF) production. These effects may be due to schisandra inhibiting the degradation of IkappaB and therefore the translocation and activation of NF-kappaB. This may indicate a potential role for schisandra in the treatment of allergy. Similarly, another study found that schisandrin decreased scratching behaviour by inhibiting the IgE-antigen complex in vivo (Lee et al 2007).

OTHER ACTIONS

Inhibits leukotriene formation

Gomisin A has been found to inhibit the biosynthesis of leukotrienes by preventing the release of arachidonic acid in vitro (Ohkura et al 1990).

Platelet-activating factor antagonist

Several lignans inhibit platelet-activating factor in vitro (Lee et al 1999).

Cardioprotective effects

Schisandrin B demonstrated protective effects against ischaemia–reperfusion-induced myocardial damage in a dose-dependent manner in an animal model (Yim & Ko 1999). The myocardial protection was associated with an enhancement in myocardial glutathione antioxidant status. Both the whole extract and gomisin A have demonstrated vasorelaxant properties in isolated rat thoracic aorta, suggesting cardioprotective effects (Park et al 2007, Rhyu et al 2006).

Schisandra may also help to reduce cholesterol. Schisandrin B (50–200 mg/kg) was co-administered with either a high lipid diet or a cholesterol/bile salts mixture in vivo (Pan et al 2008). Hepatic total cholesterol and triglyceride levels were reduced by up to 50% and 52%, respectively as compared to control animals.

Antitumour

Extracts of schisandra have demonstrated anticancer activity against various cancer lines, including leukaemia and lung in vitro (Lin et al 2008, Min et al 2008). An in vivo study investigated the effects of schisandra in 70 rats with induced hepatocellular carcinoma over 28 days. The extract was found to effectively suppress the proliferation of the cancer cells (Loo et al 2007).

Neuroprotective

Preliminary in vitro data suggest that certain lignans from schisandra are protective against L-glutamate-induced neurotoxicity in rat cortical cells (Kim et al 2004). Schisandrin B (1–30 mg/kg for 15 days) has been shown to improve the outcome in a cerebral ischaemia/reperfusion model

in vivo (Chen et al 2008). The extract protected against damage by enhancing the cerebral antioxidant status.

Schisandrin B appears to improve cognition and hepatic functions in mice treated with tacrine, the common Alzheimer's dementia medication (Pan et al 2002). Schisandrin demonstrated the ability to reverse hyoscine-induced memory impairment in vivo by enhancing cholinergic function (Egashira et al 2008).

Bone mineralisation

Lignans isolated from the fruit and seeds of schisandra may be able to protect against bone loss. An in vitro study using UMR 106 cells demonstrated that the lignans (extracted in 95% ethanol) stimulated the proliferation and activity of alkaline phosphatase in osteoblasts (Caichompoo et al 2009).

Cytochromes and P-glycoprotein

Conflicting in vivo data suggest that certain constituents from schisandra, in particular gomisin C, may inhibit CYP450 3A4 activity (Iwata et al 2004). Various lignans from schisandra, including schisandrol A, gomisin A, schisandrin A and schisandrin B have demonstrated an inhibitory effect on P-glycoprotein in vitro (Fong et al 2007, Wan et al 2006, Yoo et al 2007, Pan et al 2006, Qiangrong et al 2005). The clinical importance of this is as yet unknown.

CLINICAL USE

The therapeutic activity of schisandra has not been significantly investigated under clinical trial conditions, so evidence is derived from traditional, in vitro and animal studies.

Liver damage, hepatoprotection

Traditionally, schisandra has been used to treat a variety of liver disorders. Hepatoprotective effects have been observed in test tube and animal studies; however, the clinical significance of these findings in humans remains unknown. Several encouraging clinical reports using an analogue of schisandrin C are available; however, it is not known whether these effects will be seen with *S. chinensis* (Akbar et al 1998). A pilot clinical study in 10 healthy subjects has evaluated the effects of schisandra and sesamin (a constituent of sesame oil) on blood fluidity due to the link between blood viscosity and liver dysfunction (Tsi & Tan 2008). The mixture was given for 1 week and blood fluidity was tested over 2 weeks, including 1-week post intervention. Blood passage time was reduced by 9.0% and 9.7% at 1 and 2 weeks, respectively, showing that the effect could be sustained for at least 1 week after cessation of treatment. The exact effects of schisandra in this formula are unknown.

Adaptogen

In TCM, schisandra is viewed as an adaptogen and prescribed with other herbs to increase resistance to physical and emotional stressors and to improve allostasis (see monographs on Korean ginseng and Siberian ginseng for further information about adaptogenic activity and allostasis).

OTHER USES

Traditionally, schisandra has been used to treat chronic cough and dyspnoea, diarrhoea, night sweats, irritability, palpitations and insomnia. Based on the herb's inhibitory effects on leukotriene biosynthesis and platelet-activating factor activity and anti-inflammatory effects, it is also used for asthmatic symptoms.

Infection

Schisandra is also used in combination with other herbal medicines to treat infection. One double-blind, randomised, placebo-controlled pilot study found that a commercial product known as ImmunoGuard significantly reduced the duration, frequency and severity of attacks in patients with familial Mediterranean fever (Amaryan et al 2003). The dose regimen used was four tablets taken three times daily for 1 month. The ImmunoGuard product contains a fixed combination of *Andrographis paniculata* Nees., *Eleutherococcus senticosus* Maxim., *Schisandra chinensis* Bail. and *Glycyrrhiza glabra* L. special extracts, which are standardised for the content of andrographolide (4 mg/tablet), eleuteroside E, schisandrins and glycyrrhizin, respectively. Although these results are encouraging, it is not known to what extent schisandra contributed to the outcome.

A double-blind, placebo-controlled, randomised pilot study investigated the effects of another preparation known as Chisan (containing schisandra (51.0%), Rhodiola (27.6%) and Siberian ginseng (24.4%)) on recovery time and quality-of-life scores in patients with acute non-specific pneumonia (Narimanian et al 2005). Sixty participants were randomised to receive the standard treatment of cephazoline, bromhexine and theophylline or the standard treatment plus the herbal mixture (20 mL twice a day standardised to contain shisandrin 0.177 mg/mL and gamma-shisandrin 0.105 mg/mL) for 10–15 days. Participants in the active group reported significant improvements in recovery time and quality-of-life scores. The requirement for antibiotics was on average 2 days shorter for those participants taking Chisan. All of these herbs have been celebrated for their adaptogenic effects and this may, at least in part, be responsible for the results. The individual effects of schisandra in this formula, however, are unknown.

DOSAGE RANGE

As clinical research is lacking, the following dosages come from Australian manufacturers' recommendations.

- Dried fruit: 1.5–6 g/day.
- Liquid extract (1:2): 3.5–8.5 mL/day or 25–60 mL/week.

TOXICITY

Insufficient reliable information is available.

ADVERSE REACTIONS

Mild gastrointestinal discomfort.

SIGNIFICANT INTERACTIONS

Controlled studies are not available, so interactions are speculative.

Drugs metabolised by CYP 3A4

In vivo evidence suggests an inhibitory effect on CYP 3A4 activity, particularly for the gomisin C constituent; however, clinical studies have not yet confirmed the effect (Iwata et al 2004). Based on this observation, serum levels of drugs chiefly metabolised by CYP 3A4 may increase — observe patient.

P-glycoprotein (P-gp) substrates

Various lignans from schisandra, including schisandrol A, gomisin A, schisandrin A and B and schisandrin B have demonstrated an inhibitory effect on P-glycoprotein in vitro (Fong et al 2007, Wan et al 2006, Yoo et al 2007, Pan et al 2006, Qiangrong et al 2005); however, the effect has not been confirmed clinically. Theoretically, the bioavailability of P-gp substrates could be increased — observe patient.

CONTRAINDICATIONS AND PRECAUTIONS

Insufficient reliable information is available.

PREGNANCY USE

Insufficient information is available to establish safety.

PRACTICE POINTS/PATIENT COUNSELLING

- *S. chinensis* is popular in TCM and is used to increase resistance to physical and emotional stressors and regarded as an adaptogen.
- Traditionally, schisandra has been used to treat chronic cough and dyspnoea, diarrhoea, night sweats, irritability, palpitations and insomnia.
- It is commonly used as a liver tonic, and preliminary evidence has identified significant hepatoprotective effects.
- Schisandra exerts direct antioxidant activity and increases hepatic and myocardial glutathione levels, thereby increasing antioxidant systems within the heart and liver.
- Overall, little clinical evidence is available; therefore, much information is still speculative and based on in vitro and animal research and traditional use.

PATIENTS' FAQs

What will this herb do for me?

Schisandra is often prescribed to increase physical and emotional resilience and as a liver tonic. It has antioxidant activity, and early research suggests that it may have significant protective benefits for the liver.

When will it start to work?

This is uncertain due to insufficient research being available.

Are there any safety issues?

This is uncertain due to insufficient research being available.

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Selenium

HISTORICAL NOTE During his travels in the 13th century, Marco Polo first reported what is thought to be selenium toxicity in grazing animals. He observed that certain grazing areas in China were associated with horses developing diseased hooves (Hendler & Rorvik 2001). It is now known that parts of China have the highest selenium soil concentrations in the world and diseased hooves were likely to be due to selenium toxicity. It was not until nearly 500 years later, in 1817, that selenium was actually discovered (Tinggi 2003) and the fact that it is essential in mammals was not discovered until 1957 (Navarro-Alarcon & Lopez-Martinez 2000). In 1979, the importance of selenium in human nutrition was further reinforced when Chinese researchers reported that selenium supplementation prevented the development of Keshan disease, a cardiomyopathy seen in children living in selenium-replete areas, and New Zealand workers reported a clinical response to selenium supplementation in a selenium-depleted patient (Shils et al 2006).

BACKGROUND AND RELEVANT PHARMACOKINETICS

Selenium is an essential trace element that enters the food chain through incorporation into plants from the soil. Selenium is mainly present in the form of selenite in acid soils, which is poorly assimilated by crops, whereas for alkaline soils, it is in the form of selenate, which is more soluble and assimilated by crops. When taken in supplement form, animal and human trials demonstrate that bioavailability of organic forms of selenium (Se-methionine and Se-cysteine) is higher than that obtained for inorganic forms (selenite and selenate) (Navarro-Alarcon & Lopez-Martinez 2000).

The variation in selenium content of adult humans living in different parts of the world is testimony to the influence of the natural environment on the selenium content of soils, crops and human tissues. According to a WHO report, adults in New Zealand have approximately 3 mg selenium in their bodies compared with 14 mg in some Americans.

Selenium is readily absorbed, especially in the duodenum and also in the caecum and colon. Vitamins A, E and C can modulate selenium absorption, and there is a complex relationship between selenium and vitamin E that has not been entirely elucidated for humans (Bates 2005). Selenium enters the body in two major forms: Se-methionine, which

is derived from plants, and Se-cysteine, which is mainly derived from animal selenoproteins (Shils et al 2006). Metabolism is complex and occurs via several routes for the different selenoproteins. Se-methionine enters the methionine pool where it undergoes the same fate as methionine until catabolised. Once the selenium from Se-methionine is liberated by the trans-sulfuration pathway in the liver or kidney, it is able to be used by peripheral cells. Ingested selenite, selenate and selenocysteine are metabolised to selenide. Urinary excretion accounts for 50–60% of total excretion of selenium and homeostasis is achieved through regulation in the kidney. Volatile forms of selenium are exhaled when intake is very high and presents a significant route of excretion at this level.

CHEMICAL COMPONENTS

In human tissues, it is found as either L-selenomethionine or L-selenocysteine.

FOOD SOURCES

The most concentrated food sources are brewer's yeast, wheatgerm, meats, fish and seafood, Brazil nuts, garlic and organ meats.

DEFICIENCY SIGNS AND SYMPTOMS

Selenium deprivation reduces the activity of selenium-dependent enzymes and has widespread effects. Characteristic signs of selenium deficiency have not been described in humans, but very low selenium status is a factor in the aetiologies of a juvenile cardiomyopathy (Keshan disease) and a chondrodystrophy (Kashin-Beck disease) that occur in selenium-deficient regions of China.

Low selenium status has been associated with:

- loss of immunocompetence (Ongele et al 2002)
- increased risk of developing certain cancers (Clark et al 1998)
- reduced male fertility (Scott et al 1998, Xu et al 2003)
- poorer prognosis in HIV infection and AIDS (Baum et al 1997, Campa et al 1999)
- greater incidence of depression, anxiety, confusion and hostility (Rayman 2000)
- compromised thyroid hormone metabolism (particularly when iodine deficiency is also present) (Gartner et al 2002)
- asthma and atopy (Kadrabova et al 1996, Misso et al 1996, Omland et al 2002)
- rheumatoid arthritis (Zamamiri-Davis et al 2002)
- possibly, increased inflammatory processes (Zamamiri-Davis et al 2002)
- changes to drug-metabolising enzymes, including the cytochrome P450 system, with some activities increasing and others decreasing (Shils et al 2006).

Low selenium status may contribute to the aetiology of several diseases, while in others this state exacerbates disease progression, such as in HIV infection.

People at risk of marginal selenium deficiency include those living in areas of low environmental selenium, such as some regions of New Zealand, people receiving long-term total parenteral nutrition (TPN), alcoholics, and those with liver cirrhosis, malabsorption syndromes, cystic fibrosis, coeliac disease and AIDS.

MAIN ACTIONS

Antioxidant

Selenium is an integral part of thioredoxin reductase and the glutathione peroxidases and therefore is intimately involved in the body's antioxidant systems. These enzymes are involved in controlling tissue levels of free radical molecules and maintain cell-mediated immunity.

Chemopreventative

Chemoprotective effects of selenium have been indicated by an epidemiological relationship, by RCTs and by experimental studies of selenium and known carcinogens in the development of specific cell lines. Overall, it appears that selenium works by inhibiting important early steps in carcinogenesis.

Several mechanisms have been postulated to explain the chemopreventative effect of selenium, including protection against oxidative damage, alterations to immune and metabolic systems, alterations to carcinogen metabolism, production of cytotoxic selenium metabolites, inhibition of protein synthesis, stabilisation of genetic material facilitating DNA repair by activation of p53, inhibition of Nuclear factor-kappa B (NF-kappa B) and stimulation of apoptosis (Christensen et al 2007, Chun et al 2006, Clark et al 1996, El Bayoumy 2001, Schrauzer 2000, Seo et al 2002). One study demonstrated that combining vitamin E succinate and methylselenic acid produces a synergistic effect on cell growth suppression, primarily mediated by augmenting apoptosis (Zu & Ip 2003).

In humans, the chemopreventative effect is strongest for individuals with the lowest selenium status; however, it is still unclear whether low selenium status is implicated in the aetiology of cancer or whether it produces a state of increased susceptibility to the effects of carcinogens.

Immunomodulation

Confirmed in both animal studies and human trials, immunomodulation is in part due to improved activation and proliferation of B-lymphocytes and enhanced T-cell function (Gazdik et al 2002a, 2002b, Hawkes et al 2001, Kiremidjian-Schumacher & Roy 1998, Ongele et al 2002). Interestingly, selenium concentrations significantly decrease during stages of acute infection, suggesting increased use and/or excretion or decreased absorption during this period (Sammalkorpi et al 1988).

Thyroid hormone modulation

Selenium is required for normal thyroid hormone synthesis, activation and metabolism (Sher 2001). Three different selenium-dependent iodothyronine deiodinases (types I, II, and III) can both activate

and inactivate thyroid hormone, making selenium an essential element for normal development, growth and metabolism through the regulation of thyroid hormones.

OTHER ACTIONS

Male fertility

Selenium is required for testosterone synthesis, normal sperm maturation and sperm motility (Rayman & Rayman 2002). Two clinical studies have confirmed this association (Scott et al 1998, Vezina et al 1996) and identified selenium supplements as able to increase sperm motility. The effect of selenium in spermatogenesis may be due to several mechanisms, including the activity of the selenium-dependent enzyme phospholipid hydroperoxide glutathione peroxidase (GPx4) (Flohe 2007), altering oxidative stress-mediated apoptosis in germ cells (Kaushal & Bansal 2007a, 2007b), and the modulation of transcription factor NF-kappaB (Shalini & Bansal 2006, 2007a). Interestingly, animal studies suggest that detrimental effects on fertility are associated with either too little or excessive selenium intake (Shalini & Bansal 2007b, 2008).

Anti-inflammatory

Selenium deficiency produces a significantly increased COX-2 protein expression, as well as higher PGE_2 levels, according to one in vitro study (Zamamiri-Davis et al 2002). It has also been theorised that selenium may decrease leukotriene production (McCarty 1984). In vivo tests have identified anti-inflammatory activity in the lung with selenium, which is thought to relate to an increase in glutathione levels and immune parameters (Jeong et al 2002).

Reduces heavy metal toxicity

Selenium protects against toxicity of some heavy metals, such as cadmium, arsenic, lead, silver and mercury (Berry & Galle 1994, Bolkent et al 2008, Chuang et al 2007, El-Sharaky et al 2007, El-Shenawy & Hassan 2008, Lindh et al 1996, Navarro-Alarcon & Lopez-Martinez 2000, Yiin et al 1999a, 1999b, 2000, 2001). A physiological role for selenium in counteracting heavy metal poisoning has been proposed (Shils et al 2006). It appears that the form of selenium is important, as inorganic selenium has been shown to enhance the toxic effects of inorganic arsenic by increasing its retention in tissues and suppressing its metabolism in vitro (Styblo & Thomas 2001).

Antiatherogenic activity

Selenium supplementation reduces high-fat diet-induced atherosclerosis, according to an in vivo study (Kang et al 2001). In healthy subjects fed a test meal high in lipid hydroperoxides, selenium supplementation counteracted the postprandial synthesis of the atherogenic form of LDL (Natella et al 2007). According to studies with experimental models, beneficial effects on lipid metabolism are due to significant up-regulation of LDL receptor activity and mRNA expression (Dhingra & Bansal 2006a), and down-regulation of hypercholesterolaemia-induced changes in apolipoprotein B (apoB) and 3-hydroxy 3-methylglutaryl coenzyme A (HMG-CoA) reductase expression during experimental hypercholesterolaemia (Dhingra & Bansal 2006b).

CLINICAL USE

Deficiency states: prevention and treatment

Traditionally, selenium supplementation has been used to treat deficiency or prevent deficiency in conditions such as malabsorption syndromes. In addition, the elderly are at increased risk of selenium deficiency. Poor levels are negatively associated with subjective indicators of quality of life (QOL) in older people, such as self-perceived health, chewing ability, physical activity (Gonzalez et al 2007), muscle strength (Beck et al 2007, Lauretani et al 2007) and cognitive function (Akbaraly et al 2007, Gao et al 2007). Supplementation in this population where deficiency has been demonstrated is warranted.

Cancer: prevention and possible adjunct to treatment

Selenium supplementation is used to reduce total cancer incidence and mortality.

Chemoprevention

Collectively, geographical studies, epidemiological data, laboratory bioassays, studies in over 12 different animal models and human intervention trials generally support a protective role for selenium against the development of cancer; however, results are not always consistent. Further research is required to better determine characteristics of responders, optimal dosage and dose forms. Populations who live in low-selenium environments and have low selenium intakes tend to have higher cancer mortality rates. However, the results from epidemiological studies have been less consistent and show that the effect may be strongest in males.

Total cancer incidence and mortality

The Nutritional Prevention of Cancer (NPC) Trial was a large multicentre, double-blind, randomised, placebo-controlled trial conducted with 1312 patients with a history of basal cell or squamous cell carcinomas of the skin, which investigated the effects of 200 microgram selenium daily (as 500 mg brewer's yeast) as a cancer protective agent (Clark et al 1998). Selenium supplementation in this population did not alter future incidence of skin cancer; however, it significantly reduced total cancer mortality, total cancer incidence by 37% and the incidences of lung, colorectal and prostate cancers by 46%, 58% and 63%, respectively. Results from further continuation of the trial have continued to find a protective effect for selenium in total cancer incidence and the individual cancers; however, this now appears to be restricted to people with low baseline plasma levels and most pronounced for colorectal cancer and current smokers, whereas protective effects in prostate cancer was further restricted to lower baseline levels of prostate-specific antigen (PSA: ≤4 ng/mL)

(Duffield-Lillico et al 2002, 2003, Reid et al 2002, 2006). However, in a recent small randomised, double-blinded adjunct study to the NPC Trial, subjects receiving 400 microgram/day (as selenised yeast) did not have a lower total cancer incidence compared to those receiving the matched yeast placebo. Whilst selenium at 200 microgram/day lowered cancer incidence by 25%, this protective effect was not seen when a double dose was used (Reid et al 2008).

The association between selenium levels and all-cause and cause-specific mortality was recently examined in a large prospective study involving 13,887 adult participants involved in the Third National Health and Nutrition Examination Survey (NHANES III). At the 12-year follow-up, both all-cause and cancer mortality were found to be reduced with increasing serum selenium levels up to <130 ng/mL, but a gradual increase in mortality was seen at higher levels exceeding 150 ng/mL (Bleys et al 2008).

Liver cancer

A trial involving 130,471 individuals living in a high-risk area for viral hepatitis and liver cancer (Quidong, China) found that table salt enriched with sodium selenite reduced the incidence of liver cancer by 35% during the 8-year follow-up period, whereas no changes were observed for the control groups (Yu et al 1997). Additionally, incidences of liver cancer began to rise after withdrawal of selenium supplementation. Patients with hepatocellular carcinoma had significantly lower serum selenium levels (along with iron, copper, and zinc) compared to those in the control group. The researchers speculated that lower levels of these minerals may act as biomarkers of the increased severity of viral hepatic damage (Lin et al 2006).

Prostate cancer

Epidemiological and clinical data suggest that selenium may prevent prostate cancer. A large case-control study involved 33,737 males and identified an association between higher selenium status and a reduced risk of prostate cancer (Yoshizawa et al 1998). The study showed that men consuming the most dietary selenium (assessed indirectly by measuring toenail selenium levels) developed 65% fewer cases of advanced prostate cancer than those with the lowest intake.

Strong evidence for a protective effect of selenium against prostate cancer comes from the Nutritional Prevention of Cancer (NPC) Trial, as described above, in which the incidence of prostate cancer was reduced in the selenium group by two-thirds as compared to placebo. Further follow-up has revealed that selenium supplementation continues to show a marked reduction on the incidence of prostate cancer with strongest effects seen in men with a PSA <4 ng/mL and those with the lowest serum selenium levels at study entry (Duffield-Lillico et al 2003). It is interesting to note that the NPC Trial was conducted in an area with low soil selenium content, and this may in part explain the conflicting results in studies conducted in various countries around the world.

A meta-analysis of 20 epidemiological studies found an inverse association between selenium levels (assessed in studies by serum, plasma and toenail) and risk of prostate cancer (Brinkman et al 2006). This supports the findings of an earlier meta-analysis of 16 studies (Etminan et al 2005). Similarly, in a recent prospective, case-control study (n = 130), men with newly diagnosed prostate cancer had significantly lower serum selenium compared to healthy controls (66.3 microgram/L versus 77.5 microgram/L, respectively). An increase of 10 microgram/L in serum selenium concentration was associated with a significant decrease in risk of prostate cancer (Pourmand et al 2008).

In contrast, no association between selenium and cancer has been found in some studies. Peters et al (2007) observed that there was no inverse association between prediagnostic serum selenium concentration and the risk of prostate cancer in a large cohort study with 724 cases and 879 matched controls in a nested case-control study. However, higher serum selenium levels may reduce prostate cancer risk in men who reported a high intake of vitamin E, in multivitamin users and in smokers (Peters et al 2007). Another prospective cohort study, the Vitamins And Lifestyle (VITAL) study, investigated the association of vitamin E and selenium supplementation with prostate cancer. No association was found between long-term selenium supplementation (average of 10 years) and prostate cancer risk with an average intake of >50 microgram/day compared to non-users. Supplementation for longer than an average of 10 years, however, was associated with a statistically non-significant reduction in prostate cancer among older men (≥70 years) (Peters et al 2008). Hopefully, the controversy may become clearer with the results from the currently underway Selenium and Vitamin E Cancer Prevention Trial (SELECT), which is a randomised, prospective, double-blind study designed to determine whether 200 microgram L-selenomethionine, 400 mg of racemic alpha-tocopheryol and an optional multivitamin containing no selenium or vitamin E can reduce the risk of prostate cancer among healthy men. It is anticipated that over 32,000 men will be involved in the study and final results will be available in 2013 (Klein et al 2001).

High-grade prostatic intraepithelial neoplasia (HGPIN) is the key premalignant lesion for prostate cancer. In a randomised, placebo-controlled trial, the role of selenium 200 microgram/day (in the form of selenomethionine) in preventing prostate cancer in men with HGPIN is currently being undertaken. The results of this 3-year study are due in 2009 (Marshall et al 2006).

Stomach and oesophageal cancers

A large study of nearly 30,000 people demonstrated a protective effect for a combination of selenium, beta-carotene and vitamin E against the development of cancer of the gastric cardia and oesophagus (Mark et al 2000). Supplementation also reduced the cancer mortality rate compared with those not receiving supplementation. Protective effects on total cancer deaths developed slowly, appearing

after 1 year of treatment and the effect on stomach cancer appeared after 2 years. Gene–selenium interactions may influence an individual's susceptibility to oesophageal cancer. Individuals with polymorphisms in aldehyde dehydrogenase-2 Lys/Lys, X-ray repair cross-complementing 1 399Gln/Gln or Gln/Arg alleles, glutathione S-transferase isoenzyme Ile/Ile genotype or p53 (tumour suppressor gene) Pro/Pro genotype who consumed a low-selenium diet were at the greater risk of oesophageal squamous cell carcinoma, especially when combined with tobacco and alcohol intake (Cai et al 2006a, 2006b).

The protective role of selenium on gastric cancer risk may occur only in those with low baseline selenium. In a recent study where the levels of selenium were relatively high in both cases and controls, the lowest risk of gastric cancer was found in those with the lowest quartile of selenium level (assessed by toenail levels), whereas those with the highest risk were in the second highest quartile (Koriyama et al 2008).

Colorectal cancer

The incidence of colorectal adenomas, the precursor to most colorectal cancers, may be reduced by selenium. An inverse association between selenium and adenomas has been found in numerous studies, particularly among smokers and those with low baseline serum or plasma selenium (Clark et al 1993, Connelly-Frost et al 2006, Fernandez-Banares et al 2002, Jacobs et al 2004, Peters et al 2006, Reid et al 2006, Russo et al 1997). However, others have reported no association in risk (Early et al 2002, Wallace et al 2003). Compared to age-matched healthy controls, patients with colorectal cancer were found to have statistically lower serum selenium levels. Furthermore, a higher level of selenium was present in the cancerous tissue than in healthy tissue, though it is unclear whether this is the reason for the decreased selenium in the serum or whether the decreased serum levels occur prior to the development of colorectal cancer (Charalabopoulos et al 2006).

Premalignant skin lesions

Increased selenium status may reduce the incidence of arsenic-related premalignant skin lesions (Chen et al 2007, Huang et al 2008). This is consistent with several observational studies that found a protective association between plasma selenium level and the risk of non-melanoma skin cancer (Breslow et al 1995, Clark et al 1984, Karagas et al 1997). Long-term selenium supplementation may exert a protective effect against arsenic-induced premalignant skin lesions by reversing some of the changes in gene expression (Kibriya et al 2007).

Female reproductive

Selenium status measured by plasma levels and erythrocyte glutathione peroxidase activity was significantly lower in patients with cancer or benign neoplasia of the reproductive tract (uterus or ovary). Furthermore, examination of tissue margins of the tumours following surgery revealed significantly higher selenium concentrations compared to healthy tissue margins of healthy tissue. This suggests a protective role of selenium in the development of these reproductive tumours and a compensatory up-regulation of antioxidant defence systems in tumours due to persistent oxidative stress (Piekutowski et al 2007).

Oral Cancer

Selenium levels are significantly associated with risk of oral squamous cell carcinoma, with lower levels found in patients compared to both healthy controls and those with precancerous lesions (oral submucous fibrosis and oral leucoplakia) (Khanna & Karjodkar 2006).

Reducing mortality from HIV infection

Selenium appears to be important in HIV infection, with plasma selenium a strong predictor of disease outcome in both adults and children (Baum & Shor-Posner 1998, Baum et al 1997, Campa et al 1999).

Low selenium status is common in HIV-positive patients and is associated with a decline in Th (CD4) cell counts (Bates 2005). In a double-blind, randomised, placebo-controlled trial, selenium supplementation (200 microgram/day) for 9 months suppressed the progression of HIV-1 viral burden and indirectly improved CD4 counts in adult HIV-infected men and women (Hurwitz et al 2007). Low selenium is also associated with an increased incidence of mycobacterial diseases in HIV-1-seropositive drug users (Dworkin 1994, Dworkin et al 1986, 1989, Shor-Posner et al 2002). One small intervention trial using low-dose selenium supplements (80 microgram/day with 25 mg vitamin E) over 2 months has shown an improvement in general symptoms but no alterations to immunological or haemotological parameters (Cirelli et al 1991).

The protective role of selenium in HIV-infected pregnant women is less clear. One study found that low plasma selenium status was associated with increased risk of intrapartum transmission of HIV, risk of fetal and child mortality and the risk of small-for-gestational age (Kupka et al 2005). In contrast, in a recent randomised, double-blind, placebo-controlled trial, 200 microgram/day of selenium during and after pregnancy did not improve HIV disease progression, fetal mortality, prematurity or small-for-gestational age birth. Supplementation may however improve child survival after 6 weeks (Kupka et al 2008).

Selenium and selenium-dependent glutathione peroxidase (GSH-Px) are important for antioxidant protection and reducing oxidative damage in HIV. Antioxidant defences are increased in selenium-replete HIV patients due to the increase in oxidative stress induced by the infection (Stephensen et al 2007). However, in those with poor selenium levels and subsequently reduced GSH-Px defences, the increased oxidative stress may increase HIV progression (Ogunro et al 2006).

Cardiovascular disease prevention

Selenium may decrease cardiovascular disease mortality; however, epidemiological studies have produced mixed results. A meta-analysis examining the

relationship between selenium and coronary heart disease found an overall positive effect in observational studies (11 out of 14 cohort studies and 9 of 11 case-control studies). A 50% increase in selenium concentrations was associated with a 24% reduced risk of coronary events. However in the randomised controlled trials, supplementation with selenium (4 out of 6 trials using multiple nutrients) had only a non-significant 11% reduction in coronary events (Flores-Mateo et al 2006).

In contrast, no significant primary preventative effect was seen for selenium supplementation (200 microgram/day) and incidence of cardiovascular disease, myocardial infarction, stroke or all cardiovascular disease mortality in the NPC study (Stranges et al 2006). Lack of association was confirmed when analyses were further stratified by tertiles of baseline plasma selenium concentrations.

An individual's selenium status may play an important role in its effectiveness in attenuating cardiovascular disease, with both too little and too much increasing risk. In a recent study, Bleys et al (2008) found that while cardiovascular and coronary heart disease mortality decreased as serum selenium levels increased up to levels of 120 ng/mL, at levels above this the mortality risk was not statistically increased (Bleys et al 2008). Many of the studies investigating selenium and cardiovascular disease have been conducted in European countries that have a lower selenium intake compared to countries such as the United States. It is possible that selenium is most effective at preventing cardiovascular disease in areas with intake levels less than those in the United States (Bleys et al 2008).

The correlation between selenium status and cardiovascular disease may be stronger in the elderly who typically have lower selenium levels. In a 9-year longitudinal study, the decline in selenium associated with ageing was greater in those who were obese or had experienced cardiovascular events (Arnaud et al 2007), suggesting that a greater intake may be necessary in these individuals to counter oxidative stress.

With regard to secondary prevention, an intervention study conducted by Korpela et al (1989) in subjects having suffered from acute myocardial infarction has produced encouraging results. The randomised, double-blind trial compared the effects of selenium-rich yeast (100 microgram/day) with placebo, concurrently with standard treatment in 81 patients with acute myocardial infarction. During the 6-month follow-up period, there were no cardiac deaths in the selenium-treated group compared with four receiving placebo, and two non-fatal re-infarctions in the placebo group compared with only one receiving selenium supplementation.

Low selenium status may contribute to the development of hypertension. In a cross-sectional longitudinal study involving 710 Flemish subjects with an average baseline blood pressure of 130/77 mmHg, an inverse relationship was found between blood selenium and blood pressure in men at follow-up (median of 5.2 years). A 20-microgram/L higher baseline blood selenium concentration was associated with a 37% lower risk of developing high-normal BP or hypertension. No association was found in women (Nawrot et al 2007).

Compared to premenopausal women, postmenopausal women had lower erythrocyte selenium levels, which were associated with significantly higher levels of total cholesterol, triglycerides and LDL cholesterol. This association remained after controlling for age, smoking status and body mass index (Karita et al 2008).

Diabetes

The relationship between selenium and diabetes is complex. Selenium appears to be involved in several key aspects of pancreatic beta-cell and islet function, increasing insulin content and secretion (Campbell et al 2008). Compared to healthy controls, diabetic patients have been found to have lower selenium levels (assessed by toenail levels) (Rajpathak et al 2005). Supplementation with selenium in diabetic patients has been found to reduce activation of NF-kappa B and levels of oxidative stress, and thus may help to prevent vascular complications (Faure et al 2004). Selenium has also been found to inhibit high glucose- and high insulin-induced expression of adhesion molecule via modulation of p38 pathway, and may therefore help to prevent the development of atherosclerosis in diabetics (Zheng et al 2008). However, recent data suggest that chronically high-selenium levels in selenium-replete populations may increase the risk of developing diabetes. Results from the NHANES III found that those in the highest quintile of serum selenium had a statistically significant increased prevalence of diabetes compared with those in the first quintile (Bleys et al 2007). Similarly, secondary analysis of the NPC trial found that 200 microgram/day of selenium for an average of 7.7 years did not prevent diabetes and statistically significantly increased the risk of type 2 diabetes compared to the placebo group (Stranges et al 2007).

Selenium may play a protective role in gestational diabetes. A cross-sectional study involving 178 pregnant women (24–28 weeks of gestation) found a significant inverse correlation between selenium and blood glucose levels in patients with gestational diabetes mellitus or glucose intolerance having lower serum selenium levels compared to healthy controls (Kilinc et al 2008). This supports similar findings (Al-Saleh et al 2004, 2007, Bo et al 2005, Hawkes et al 2004, Molnar et al 2008, Tan et al 2001).

Asthma

Asthma, respiratory symptoms and ventilatory function have been associated with lowered circulatory selenium status and glutathione peroxidase activity (Devereux & Seaton 2005, Hasselmark et al 1990, Kadrabova et al 1996, Misso et al 1996, Omland et al 2002). When these observations are coupled with in vivo evidence of anti-inflammatory activity in the lung for selenium, it is not surprising that there is growing interest in using selenium supplementation to improve asthmatic symptoms and disease management. A small number of intervention studies have been conducted, producing mixed results (Gazdik et al 2002a, 2002b, Hasselmark et al 1993).

Hasselmark et al conducted a randomised, double-blind study involving 24 patients with intrinsic asthma. A dose of 100 microgram sodium selenite was administered for 14 weeks, resulting in significant increases in serum selenium and platelet glutathione peroxidase activity, while no changes were observed with placebo. Clinical results varied, with significantly more treated patients improving on several parameters of lung function, such as airway responsiveness, clinical examination, medication use and subjective patient impressions. However, there were no significant improvements over baseline in any individual clinical parameter. A small pilot study of 17 asthmatics dependent on corticosteroid medication found that a dose of 200 microgram selenium daily taken over a 96-week period reduced both inhaled and systemic corticosteroid requirements. The same study observed selenium supplementation enhancing immunity (Gazdik et al 2002a, 2002b).

Results from several recent studies have not demonstrated a beneficial effect of selenium in asthma. Meta-analysis of data from a recent case-control study involving 569 asthmatic patients and 576 healthy controls in 14 European centres found no overall effect between plasma selenium levels and the risk of asthma. There was heterogeneity in results among the centres, however with a 10 microgram/L increase in plasma selenium associated with a 52% decreased risk of asthma in Lodz, but a 35% increase in risk in Ghent and a 68% increase in risk in Amsterdam (Burney et al 2008). These results are similar to those from a randomised, double-blind, placebo-controlled trial involving 197 asthmatic subjects given either a selenium supplement (high-selenium yeast preparation of 100 microgram) daily or placebo for 6 months. Whilst the baseline plasma selenium levels increased by 48% in the treatment group, there was no significant difference between the groups with regard to either the primary outcome (asthma-related QOL score) or secondary outcomes, including lung function, asthma symptom scores, peak flow and bronchodilator usage (Shaheen et al 2007).

Selenium appears to have a protective role in reducing childhood wheezing. Low plasma selenium levels during early pregnancy and in the neonate have been found to increase the risk of early childhood wheezing, although this positive association was no longer found at the age of 5 (Devereux et al 2007). Similarly in a study of 61 children aged 0.3–5 years with no atopic history, lower serum selenium levels were found in those with frequent wheezing compared with those in healthy controls, and selenium levels were significantly correlated with the number of wheezing episodes experienced in the previous year. This protective effect may be due to preventing the progression of respiratory infections which subsequently contribute to the development of wheezing (Kocabas et al 2006).

Autoimmune thyroiditis

Selenium appears to play an important role in the health of thyroid gland function and the prevention of disease. In a study of differences in selenium levels between those with thyroid disease and those without, selenium levels were significantly decreased in those with both benign thyroid disease (subacute and silent thyroiditis) and malignant thyroid disease (follicular and papillary thyroid carcinoma) compared to healthy controls (Moncayo et al 2008). Similarly in a study of patients with Graves' disease, those with the highest serum selenium levels (>120 microgram/L) were more likely to be in disease remission (Wertenbruch et al 2007).

Selenium supplementation may improve inflammatory activity in chronic autoimmune thyroiditis patients, as evidenced by a significant reduction in the concentration of thyroid peroxidase antibodies (TPO-Ab) to 63.8% in selenium-supplemented subjects versus 88% ($P = 0.95$) in placebo subjects (Gartner et al 2002). The randomised study of 70 females (mean age 47.5 years) compared 200 microgram sodium selenium daily orally for 90 days to placebo. A follow-up crossover study of 47 patients from the initial 70 was conducted for a further 6 months (Gartner & Gasnier 2003). The group that continued to take sodium selenite (200 microgram/day) experienced further significant decreases, whereas the group that ceased selenium use experienced a significant increase. The patients who received 200 microgram sodium selenite after placebo also experienced a significant decrease in levels of TPO-Ab. More recently, in a prospective study of 80 patients with Hashimoto's thyroiditis receiving 200 microgram selenium (as selenomethionine) resulted in a significant 9.9% decrease in TPO-Ab levels after 6 months. In those patients who continued to take the selenium for another 6 months, TPO-Ab levels decreased by another 8% whilst those who ceased treatment experienced a 4.8% increase (Mazokopakis et al 2007). The role of selenium in the treatment of autoimmune thyroiditis (AIT) may be limited to those with a higher level of disease activity. In consecutive AIT patients randomised to receive 200 microgram/day of selenium for 3 months in addition to levothyroxine medication, there was no significant decrease in TPO-Ab levels or difference in cytokine patterns compared to either pre-treatment levels or those in the placebo group (Karanikas et al 2008). The authors suggest that the lack of effect in this study may be due to the lower initial TPO-Ab levels compared to those reporting positive results, such as the studies above.

In a study investigating the efficacy of 100 microgram and 200 microgram doses of selenomethionine in reducing serum concentrations of TPO-Ab in patients with AIT, Turker et al (2006) concluded that the larger dose was more effective (Turker et al 2006).

Selenium supplementation (200 microgram/day) during and after pregnancy inhibits the post-partum progression of autoimmune chronic thyroiditis in those with positive thyroid peroxidase antibodies. In a prospective, randomised, placebo-controlled study, patients supplemented with selenium had significantly reduced thyroid inflammatory activity and the incidence of hypothyroidism compared to those receiving no treatment (placebo) (Negro et al 2007).

Rheumatoid arthritis (RA)

Selenium supplements have been used in RA because of its antioxidant activity and the observation that some patients with RA have been reported with low selenium status (O'Dell et al 1991, Rosenstein & Caldwell 1999). One double-blind, placebo-controlled intervention study of 55 patients with moderate RA found that both placebo and selenium appeared to have significant effects on a number of symptoms; however, only selenium significantly improved arm movements and sense of wellbeing (Peretz et al 2001).

Lowered male fertility

Xu et al (2003) identified a significantly positive correlation between selenium levels and sperm density, sperm number, sperm motility and sperm viability in human volunteers. Similarly, Akinloye et al (2005) reported a significant inverse correlation between serum selenium level and sperm count and serum testosterone, and seminal plasma selenium with spermatozoa motility, viability and morphology (Akinloye et al 2005). Supplementation with selenium in selenium-replete subfertile men has been shown to improve sperm motility and the chance of successful conception in over half of treated patients (Scott et al 1998). When taken with vitamin E over 6 months, selenium produces a statistically significant increase in sperm motility, percent live and percent normal spermatozoa, with effects reversing after supplement cessation (Vezina et al 1996). Although results are encouraging, particularly for subfertile men with low selenium status, one negative intervention trial was located that found that supplementation had no effect (Iwanier & Zachara 1995).

General immune enhancement

Several intervention trials of either double-blind or open design have shown that selenium supplementation can enhance immune function and decrease the risk of developing certain infections in selenium-replete subjects, healthy adults and the elderly (Girodon et al 1999, Kiremidjian-Schumacher et al 1994, Roy et al 1994, Yu et al 1989).

The largest was a 3-year study of 20,847 people that showed that substituting conventional table salt with table salt fortified with sodium selenite significantly reduced the incidence of viral hepatitis compared with controls provided with normal table salt (Yu et al 1989).

Critically ill patients

Selenoproteins play an important role in the immunomodulation of critically ill patients, and low levels of plasma selenium have been associated with increased markers of oxidative stress, risk of organ failure and higher mortality rates. Clinical trials of selenium supplementation in critically ill patients however have produced mixed results. In a prospective, randomised, placebo-controlled, multicentre trial, critically ill patients received 1000 microgram of sodium selenite as a 30-min bolus injection, followed by 14 daily continuous infusions of 1000 microgram intravenously, or placebo. After 28 days, mortality rate was reduced in the treatment group to 42.4% compared with 56.7% in the placebo group. The mortality rate was significantly reduced in patients with septic shock or severe sepsis (Angstwurm et al 2007). In contrast, a prospective, multicentre, placebo-controlled, randomised, double-blind study of 60 patients with severe septic shock and infection found that the mortality rate of those receiving selenium supplementation (4000 microgram sodium selenite on the first day, 1000 microgram/day on the 9 following days) did not differ significantly from the placebo group (Heyland 2007). A prospective, single-centre study involving 40 septic ICU patients found that high-dose selenium supplementation (474, 316, 158 microgram/day, each for 3 consecutive days followed by a standard dose of 31.6 microgram/day given as sodium selenite) did not reduce oxidative damage or the requirement for renal replacement therapy (Mishra et al 2007). One possible explanation suggested for negative findings is sodium selenite having a direct pro-oxidant action in these patients (Forceville 2007).

Mood elevation and reduced anxiety

Considering that low dietary intakes of selenium have been linked with greater incidence of anxiety, depression and tiredness, several research groups have investigated whether higher dietary intakes or selenium supplementation will elevate mood and/or reduce anxiety. Currently, results are equivocal; however, it appears that selenium-replete individuals are most likely to respond to supplementation, if a response is observed.

An early double-blind, crossover study showed that short-term selenium supplementation (100 microgram/day for 5 weeks) significantly elevated mood and decreased anxiety, depression and tiredness, with effects most marked in people with low dietary intake (Benton & Cook 1991). A study of 30 selenium-replete men who were fed either a low (32.6 microgram/day) or a high (226.5 microgram/day) selenium diet for 15 weeks found that the mood of those with the higher selenium intake increased, whereas mood worsened with low intake (Finley & Penland 1998 as reported in Rayman 2005). Alternatively, another study involving 11 men of adequate selenium intake failed to show effects on mood when high (356 microgram/day) and low (13 microgram/day) selenium diets were followed for 99 days (Hawkes & Hornbostel 1996). Most recently, a large (n = 448), 2-year, randomised study also failed to find evidence that additional selenium enhanced mood or any of its subscales, despite significant increases in plasma selenium levels (Rayman et al 2006). This study compared the effects of 100, 200 or 300 microgram/day of selenium to placebo for effects on mood and QOL. Selenium supplementation was given as high-selenium yeast, SelenoPrecise™ (Pharma Nord, Vejle, Denmark).

Reducing morbidity in preterm babies

Preterm infants are born with slightly lower selenium and glutathione peroxidase concentrations than term infants and have low hepatic stores

of selenium. In very preterm infants, low selenium concentrations have been associated with an increased risk of chronic neonatal lung disease and retinopathy of prematurity (Darlow & Austin 2003). Although the full consequences of low selenium concentrations in this population are not fully known, observation from animal studies has found an association between selenium deficiency and increased susceptibility to oxidative lung injury. This has special significance for sick, very preterm infants as they are exposed to many possible sources of oxygen radical products, including high concentrations of inspired oxygen. A Cochrane review of three randomised studies that reported outcomes on 297 infants receiving selenium supplements and 290 control infants concluded that selenium supplementation in very preterm infants is associated with benefit in terms of a reduction in one or more episodes of late-onset sepsis, but is not associated with improved survival, a reduction in neonatal chronic lung disease or retinopathy of prematurity (Darlow & Austin 2003). It should be noted that most of the evidence derives from research conducted in New Zealand, a country with low soil and population selenium concentrations, and may not be readily translated to other populations. In one study, despite preterm infants having lower selenium levels compared to term infants, selenium levels did not correlate with chronic lung disease or septicaemia (Loui et al 2008).

OTHER USES

Used in combination with other antioxidants or administered intravenously, selenium has been used in pancreatitis and as adjunctive therapy in cancer patients.

Oral sodium selenite (350 microgram/m^2 body surface area) was given daily for 4–6 weeks to 52 patients with extensive, persistent or progressive lymphoedema from radiation and resulted in the majority experiencing some reduction in oedema (Micke et al 2002). A further study (Micke et al 2003) of 48 patients found that sodium selenite supplementation had a positive effect on secondary lymphoedema caused by radiation therapy alone or by irradiation after surgery. The group consisted of 12 patients with oedema of the arm and 36 with oedema of the head and neck region.

Cancer treatment often induces toxicity associated with the oxidative damage to normal cells. A Cochrane review of selenium in the prevention of side effects associated with cancer treatment (Dennert & Horneber 2006) found only two trials that met inclusion criteria. One study found lower incidence of recurrent erysipela infections of lymphoedematous upper limbs after breast cancer treatment in the selenium group, whilst preliminary results from another study suggest a lower incidence of diarrhoea in those receiving pelvic radiotherapy.

In an animal model, moderate selenium supplementation increased the total antioxidant activity leading to a lower generation of reactive oxygen metabolites, which helped to counteract the cardiotoxicity associated with the chemotherapeutic drug adriamycin (Danesi et al 2006).

DOSAGE RANGE

The Therapeutic Goods Act altered the allowed amount of selenium in listed products to be raised to 150 microgram. Supplements containing selenium carry the following caution on their label: 'This product contains selenium which is toxic in high doses. A daily dose of 150 microgram for adults of selenium from dietary supplements should not be exceeded.'

Australian RDI

Children
- 1–3 years: 25 microgram
- 4–8 years: 30 microgram
- 9–13 years: 50 microgram
- 14–18 years:
  Boys: 70 microgram
  Girls: 60 microgram

Adults
- Males >18 years: 70 microgram
- Females >18 years: 60 microgram
- Pregnancy: 65 microgram
- Lactation: 75 microgram

According to clinical studies

- Asthma: 100–200 microgram/day of sodium selenite.
- Cancer prophylaxis: 200 microgram/day selenium (supplied as 500 mg brewer's yeast).
- Infertility: 100 microgram/day.
- Mood disturbances: 100 microgram/day.
- Post myocardial infarction: selenium-rich yeast 100 microgram/day.
- Rheumatoid arthritis: 200 microgram/day.
- Autoimmune thyroiditis: 200 microgram/day sodium selenite.
- HIV-positive status: 80 microgram/day has been used but it is most likely that higher doses are required.

TOXICITY

Long-term ingestion of excessive levels of selenium (>1000 microgram/day) may produce fatigue, depression, arthritis, hair or fingernail loss, garlicky breath or body odour and gastrointestinal disorders or irritability (Fan & Kizer 1990).

ADVERSE REACTIONS

Nausea, vomiting, nail changes, irritability and fatigue have been reported.

The organic form of selenium found in high-selenium yeast is often preferred because it is less toxic.

The National Health and Medical Research Council of Australia states that selenium intake should not exceed 600 microgram/day.

SIGNIFICANT INTERACTIONS

Cisplatin

Selenium may reduce associated nephrotoxicity, myeloid suppression and weight loss, according to in vitro and in vivo tests (Camargo et al 2001, Ohkawa et al 1988) — potentially beneficial interaction.

Heavy metals (e.g. mercury, lead, arsenic, silver and cadmium)

Selenium reduces toxicity of heavy metals such as mercury, lead, arsenic, silver and cadmium by forming inert complexes — beneficial interaction.

CONTRAINDICATIONS AND PRECAUTIONS

Sensitivity to selenium.

PREGNANCY USE

Considered safe in usual dietary doses; safety at higher levels is unknown.

PRACTICE POINTS/PATIENT COUNSELLING

- Selenium is a trace element that is essential for health.
- Low selenium states have been associated with a variety of conditions such as cardiovascular disease, cancer, asthma, atopy, male subfertility, rheumatoid arthritis, depression and anxiety and compromised immune function.
- Studies have identified selenium deficiency in a significant number of people with the HIV infection and suggested a link between selenium levels and mortality rate.
- It is also involved in the detoxification of some heavy metals and xenobiotics.
- Selenium-enriched yeast is the safest way to supplement the diet, but other forms are also used.

PATIENTS' FAQs

What will this supplement do for me?

Selenium supplementation may reduce the risk of developing certain cancers and heart disease and help to improve a range of conditions such as rheumatoid arthritis, asthma, autoimmune thyroiditis, male subfertility, depression and anxiety.

When will it start to work?

If a protective effect is to occur with selenium against cancer or cardiovascular disease, the effect appears to develop slowly over several years' consistent intake.

Are there any safety issues?

High intakes of selenium above 1000 microgram/day have been associated with a number of adverse effects and should be avoided.

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Shark cartilage

HISTORICAL NOTE Shark cartilage became a popular supplement in the 1980s, largely based around the claim that sharks rarely get cancer and therefore must have some protection against the disease. By 1995, the annual world market for shark-cartilage products exceeded US$30 million and dozens of shark cartilage products were available in retail stores and usually sold as food supplements (Ernst 1998). Over the past few decades, some progress has been made in identifying the various unusual compounds present in shark cartilage and it is clearly known that it contains some anti-angiogenic compounds, which increase resistance to tumours. Numerous shark cartilage derivatives and extracts are currently being investigated for effects on tumours including squalamine lactate, AE-941 and U-995. Previously, much work had been conducted with bovine cartilage, which also exhibits anti-angiogenic properties, although to a lesser extent.

BACKGROUND AND RELEVANT PHARMACOKINETICS

Although there has been some investigation into its actions and potential role as a therapeutic agent, little information is available about its pharmacokinetics.

CHEMICAL COMPONENTS

Shark cartilage is mainly composed of proteins, calcium, phosphorus, water, collagen and proteoglycans, chiefly chondroitin sulfates. Collagen imparts tensile strength and proteoglycans impart resilience to cartilage.

MAIN ACTIONS

Analgesic and anti-inflammatory

Both analgesic and anti-inflammatory activities have been reported for shark cartilage preparations in animal studies (Fontenele et al 1996, 1997). The mechanism of action is unknown; however, tests with the opioid antagonist naloxone have found it does not involve the opioid system (Fontenele et al 1997). One mechanism of action suggested is that shark cartilage significantly inhibits IL-1-induced PGE_2 synthesis (Pearson et al 2007).

Suppression of airway inflammation, by downregulating vascular endothelial growth factor, was demonstrated in an animal model, suggesting a possible novel therapeutic application to treat bronchial asthma. This research was carried out with a marine cartilage pharmaceutical formula called Neovastat (AE-941) (Lee et al 2005, Lee & Chung 2007).

There is also research indicating shark cartilage might be useful for some but not all inflammatory conditions. A number of different commercial shark cartilage extracts were tested and found to induce TH1 type inflammatory cytokines. In addition the acid extracts of shark cartilage tested produced higher amounts of TNF (alpha) than the other aqueous extracts. As well as stimulating a TH1 response, the cartilage extracts appeared to inhibit TH2 cells, which may be useful for hypersensitive individuals who would benefit from downregulation of the IgE response (Merly et al 2007).

Anti-angiogenic

Shark cartilage extract appears to block the two main pathways that contribute to the process of angiogenesis, matrix metalloproteases and the vascular endothelial growth factor signalling pathway (Anon 2004). The effect is due to several different constituents that have been isolated from shark cartilage and identified as exerting anti-angiogenic activity (Dupont et al 1998, Gonzalez et al 2001, Shen et al 2001, Sheu et al 1998, Zheng et al 2007, Bargahi & Rabbani-Chadegani 2008, Rabbani-Chadegani et al 2008) in various experimental models.

Antineoplastic effects

Due to its anti-angiogenic activity, shark cartilage has been investigated for antineoplastic effects. In one study, oral administration of powdered shark cartilage significantly delayed the development of papillary and solid tumours in a murine renal tumour model in experimental animals (Barber et al 2001). Shark cartilage proteoglycan was found to inhibit pancreatic carcinogenesis when administered to hamsters for 50 days (Kitahashi et al 2006).

Immunostimulant

A complex mixture of constituents is responsible for the immunostimulating properties of shark cartilage, according to in vitro research (Kralovec et al 2003). Of these, a protein fraction composed of two proteins with molecular weights of approximately 14 and 15 kDa has exhibited the most immunostimulatory effects (Hassan et al 2005).

OTHER ACTIONS

Antibiotic

Squalamine, isolated from dogfish shark cartilage, is a broad-spectrum antibiotic with activity against protozoa, fungi and both Gram-positive and Gram-negative bacteria (Moore 1993).

Antioxidant

Antioxidant activity has been demonstrated in vitro (Gomes et al 1996).

Fibrinolytic

Fibrinolytic activity of a shark cartilage extract was demonstrated in an in vitro study (Ratel et al 2005).

CLINICAL USE

Osteoarthritis

Based on its analgesic and anti-inflammatory activities, shark cartilage has been used to relieve symptoms in OA. To date, no clinical studies are available to determine its effectiveness; however, positive results have been obtained in several clinical studies for one of its constituents, chondroitin sulfate (see Chondroitin monograph for details).

Cancer

Shark cartilage is a popular supplement with cancer patients (Bernstein & Grasso 2001), although results from the few clinical trials conducted using shark cartilage in people with advanced cancers have generally produced negative findings suggesting no significant benefit.

One study of 60 people with advanced, previously treated cancer (breast, colorectal, lung, prostate, non-Hodgkin's lymphoma, brain) failed to demonstrate an effect for orally administered shark cartilage (1 g/kg) on tumour growth or QOL (Miller et al 1998). A larger study of 83 patients with advanced breast and colorectal cancers, which was published in 2005, also found that shark cartilage failed to improve survival or QOL (Loprinzi et al 2005). This study was a two-arm, randomised, placebo-controlled, double-blind, clinical trial. Of note, there was a high drop-out rate as only half the patients receiving shark cartilage powder continued with treatment beyond 1 month and only 10% were still using the treatment by 6 months. It was thought that gastrointestinal symptoms may have contributed to the poor patient compliance.

Clinical note — Angiogenesis and tumour growth
Angiogenesis is defined as the formation of new capillary blood vessels from existing microvessels and is a process regulated by inducers and inhibitors. It is critical for development, reproduction and repair and dominates many pathological conditions (Folkman 2003). In 1971, the hypothesis that tumour growth is angiogenesis-dependent was first proposed and since then, the study of angiogenesis inhibitors in cancer research has developed. It has now been demonstrated that solid tumours secrete angiogenic substances to set up an internal network of blood vessels to support further growth and there is a correlation between tumour microvessel density and the risk of metastases. In the absence of angiogenesis, tumour growth is restricted to a microscopic size and tumour cells do not shed into the circulation. Several clinical studies have been conducted with various anti-angiogenic therapies, generally indicating that despite an initial increase in tumour blood flow, long-term treatment causes total tumour blood flow to reach a steady state or to gradually decrease.

Several smaller preliminary studies have produced positive results, with some patients experiencing less tumour progression and weight loss, improved appetite or decreased pain (Couzin et al 2003). Unfortunately, details of these studies are difficult to locate and much remains unanswered, such as doses used, time frames for use and criteria for improvement.

Investigation with Neovastat (AE-941), a standardised shark cartilage extract, has produced more promising results and demonstrated inhibitory effects on the growth and metastasis of tumours; however, research has mainly been conducted in animal models (Hassan et al 2005). One clinical study conducted with Neovastat did report a significant survival advantage for the patients with unresectable stage IIIA, IIIB or IV non-small-cell lung cancers receiving treatment (Hassan et al 2005).

OTHER USES
There is one case report of a man with Kaposi's sarcoma whose lesion disappeared after taking shark cartilage (3.75–4.5 g/day for 9 months) (Hillman et al 2001).

DOSAGE RANGE
- Depending on the purity of the supplement, 500–4500 mg/day in divided doses.
- Various doses of cartilage have been used in different studies, ranging from 2.5 mg to 100 g/day (Simone et al 1998).

ADVERSE REACTIONS
A clinical study of 60 patients with advanced cancer reported the most common adverse reactions as gastrointestinal, such as nausea, vomiting and constipation (Miller et al 1998).

PRACTICE POINTS/PATIENT COUNSELLING
- Shark cartilage is mainly composed of calcium, phosphorus, water, collagen and proteoglycans, chiefly chondroitin sulfates.
- Anti-angiogenic, antineoplastic, immunostimulant and broad-spectrum antibiotic activities have been reported in preliminary studies.
- Both analgesic and anti-inflammatory activities have been reported for shark cartilage preparations in animal studies, most likely due to its chondroitin content. As a result, it is used to relieve symptoms in arthritic conditions.
- It is a popular supplement among cancer patients; however, the few clinical trials conducted so far with people with advanced cancers have generally produced negative results, suggesting no benefit.
- Its use is contraindicated in people with seafood allergy, and in pregnancy. Do not use 3 weeks before and 6 weeks after surgery, or in children or teenagers still experiencing growth.

SIGNIFICANT INTERACTIONS
Controlled studies and sufficient reliable information is not available to predict or determine interactions.

CONTRAINDICATIONS AND PRECAUTIONS
- Contraindicated in people with seafood allergy.
- Do not use 3 weeks before and 6 weeks after surgery, or in children or teenagers still experiencing growth.

Hypercalcaemia
Due to the high calcium content of this supplement, it should be used with caution in people with hypercalcaemia.

PREGNANCY USE
Although not scientifically investigated in this population, it is not recommended in pregnancy or lactation based on theoretical considerations.

PATIENTS' FAQs
What will this supplement do for me?
Shark cartilage has a number of different actions, such as anti-inflammatory, antibiotic, anti-tumour and pain-relieving effects. However, these have not been confirmed in controlled human studies. As a result, it is difficult to determine what effects will be experienced.
When will it start to work?
Due to the lack of human research, this is unknown.
Are there any safety issues?
Shark cartilage products are not to be used in people with seafood allergy or in pregnancy. They should not be used by children or teenagers still experiencing growth or 3 weeks before and for 6 weeks after surgery.

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Shatavari

HISTORICAL NOTE There are approximately 300 species of 'asparagus' (derived from the Greek word for 'stalk' or 'shoot') including the popular European vegetable *Asparagus officinalis*. The medicinal use of *Asparagus racemosus* (shatavari) has been recorded in traditional systems of medicine such as Ayurveda, Unani and Siddh (Bopana & Saxena 2007). It is a different form of asparagus from the type commonly consumed as a food, which is *Asparagus officinalis*. Shatavari, meaning 'she who possesses a hundred husbands', is often considered an aphrodisiac (Sharma et al 2000) and a 'female tonic'. It is recommended in Ayurvedic texts for the prevention and treatment of gastric ulcers and dyspepsia; for threatened miscarriage and as a galactogogue; and is known as a 'rasayana' (a substance that promotes general physical and mental wellbeing by improving defence mechanisms and vitality) (Goyal et al 2003). Demand for shatavari in combination with destructive harvesting techniques and deforestation has resulted in the plant becoming 'endangered' in its natural habitat (Bopana & Saxena 2007).

OTHER NAMES

Asparagus bush, Inli-chedi, Kairuwa, Majjigegadde, Narbodh, Norkanto, Philli-gaddalu, Satavari, Satawar, Shatmuli, Shimaishadavari, Toala-gaddalu, wild asparagus

BOTANICAL NAME/FAMILY

Asparagus racemosus Willd. (family Asparagaceae [previously Liliaceae, subfamily Asparagae]) (Goyal et al 2003)

It should be differentiated from numerous other species reported in the scientific literature, including *A. acutifolius*, *A. adscendens*, *A. africanus*, *A. curillus*, *A. dumosus*, *A. filicinus*, *A. gonaclades*; and from *A. officinalis* (the stalks of which are consumed as a vegetable).

PLANT PART USED

Root

CHEMICAL COMPONENTS

Steroidal saponins (shatavarins VI-X); saponins (shatavarin I [or asparoside B], shatavarin IV [or asparinin B, a glycoside of sarsasapogenin], shatavarin V,

immunoside and schidigerasaponin D5 [or asparanin A] (Hayes et al 2008); isoflavones (Saxena & Chourasia 2001), racemofuran, asparagamine A and racemosol (Wiboonpun et al 2004), ascorbic acid (vitamin C) (Visavadiya & Narasimhacharya 2005). Sarsasapogenin and kaempferol have also been isolated from the woody portion of the roots (Bopana & Saxena 2007).

Steroidal saponins (racemosides A, B and C) have also been isolated from the fruit (Mandal et al 2006). Quercetin, rutin and hyperoside have been identified in the flowers and fruits, and diosgenin and quercetin-3 glucuronide in the leaves (Bopana & Saxena 2007).

MAIN ACTIONS

Adaptogenic (modulates stress response)

In Ayurvedic medicine herbs are usually used in combination and shatavari is used in approximately 64 Ayurvedic formulations. Research is usually conducted with herbal combinations containing shatavari, thereby making it difficult to ascertain the pharmacological and clinical effects of the individual herb (Bopana & Saxena 2007).

A polyherbal formula, known as EuMil, which contains standardised extracts of *A. racemosus* in combination with *Withania somnifera*, *Ocimum sanctum* and *Emblica officinalis*, ameliorates chronic stress-induced neurochemical perturbations and normalises noradrenaline, dopamine and 5-hydroxytryptamine (5HT) levels in animal experiments (Bhattacharya et al 2002). Other animal studies using EuMil have demonstrated attenuation of stress-induced glucose intolerance and immunosuppression, increased male sexual behaviour, and improvements in depression and cognitive dysfunction (Muruganandam et al 2002). These results were also found in a similar polyherbal known as Siotone, containing *A. racemosus*, *Withania somnifera*, *Ocimum sanctum*, *Tribulus terrestris* and shilajit (a composted plant exudate high in minerals) (Bhattacharya et al 2000). Whether these results are consistent in humans, and which herbs they are attributed to, has not yet been established.

Digestive effects

Early studies suggested that shatavari could improve digestion by increasing levels of amylase and lipase (Dange et al 1969). A small study of 8 healthy males using a cross-over design found that oral administration of dried shatavari root had similar effects on gastric emptying time to the antiemetic drug metoclopramide, a synthetic dopamine antagonist which is used in dyspepsia to promote gastric emptying (Dalvi et al 1990). Animal experiments using oral doses of shatavari have also reversed the effects of cisplatin on gastric emptying, while normalising cisplatin-induced intestinal hypermotility (Rege et al 1999).

Antiulcerogenic

Antiulcerogenic activity comparable to a standard antiulcer drug Ranitidine (30 mg/kg/day orally) has been demonstrated in rats. Treatment with a crude extract of shatavari (100 mg/kg/day orally) for fifteen days significantly reduced indomethacin (NSAID) induced ulceration when compared with the control group. The effect appeared to be related to an inhibition of hydrochloric acid and protection of the gastric mucosa (Bhatnagar & Sisodia 2006). Early studies demonstrated that shatavari could relieve pain and burning due to duodenal ulceration and proposed that these effects may be due to: an increase in the secretion and viscosity of gastric mucus; formation of a shatavari–mucus complex at the base of the ulcer, providing protection from corrosive agents; prolongation of the life span of mucosal cells and/or a cytoprotective effect similar to that of prostaglandins (Goyal et al 2003). Some of these hypotheses have been supported by further research. The antiulcerogenic effect of oral administration of a methanolic extract of fresh shatavari root (25–100 mg/kg) twice daily for 5 days was studied on different gastroduodenal ulcer models in rats (Sairam et al 2003). Doses of 50 mg/kg twice daily demonstrated significant protection against acute gastric ulceration induced by 'cold restraint stress, pyloric ligation, aspirin plus pyloric ligation, and duodenal ulcers induced by cysteamine' and promoted healing of acetic acid-induced chronic gastric ulceration after 10 days of treatment. An effect was not demonstrated for aspirin- or ethanol-induced gastric ulcers. The effect was believed to be due to an increase in mucus secretion, cellular mucus, the life span of cells, as well as a significant anti-oxidant effect (Sairam et al 2003).

Immunomodulation

In in vitro studies *A. racemosus* increased the phagocytic and killing capacity of macrophages in a dose dependent manner (up to 200 mg/kg) (Rege & Dahanukar 1993). Experimental models in mice have demonstrated the immunostimulating properties of *A. racemosus,* inhibiting the leucopaenia associated with cyclophosphamide by inducing leucocytosis with neutrophilia (Thatte & Dahanukar 1988). Animal studies have demonstrated that oral administration of *A. racemosus* inhibited some of the deleterious effects of ochratoxin A suppression of chemotactic activity and production of IL-1 and TNF-alpha by macropahges, and also induced excess production of TNF-alpha in animals that did not receive ochratoxin A (Dhuley 1997). It also appears to reduce intraperitoneal adhesions induced by caecal rubbing by increasing the activity of macrophages (Rege et al 1989), and may act as an immunoadjuvant in animals immunised with diphtheria, tetanus, pertussis (DTP) vaccine, increasing antibody titres to *Bordetella pertussis* and providing improved immunoprotection on challenge (Gautam et al 2004).

Antibacterial

In vitro studies using different concentrations (50, 100, 150 microgram/mL) of the methanolic extract of shatavari root demonstrated considerable antibacterial efficacy against: *Escherichia coli*, *Shigella dysenteriae*, *Shigella sonnei*, *Shigella flexneri*, *Vibrio cholerae*, *Salmonella typhi*, *Salmonella typhimurium*, *Pseudomonas putida*, *Bacillus subtilis* and *Staphylococcus*

aureus (Mandal et al 2000b). A constituent of *A. racemosus* fruit, racemoside A, exhibits potent anti-leishmanial activity (Dutta et al 2007) against the dangerous visceral form of leishmaniasis.

Hormonal activity

The steroidal saponins (shatavarins) contained in *A. racemosus* may help explain some of the hormonal effects demonstrated in animal models. An alcoholic extract of Shatavari root (300 mg/kg bodyweight) was administered orally to pregnant female albino rats during days 1–15 of gestation. The results suggested an oestrogenic effect on the mammary glands and genital organs (Pandey et al 2005). Tests with animal models indicate shatavari competitively blocks the effect of oxytocin, thereby inhibiting oxytocin-induced uterine contraction in rabbits, rats and guinea pigs (Gaitonde & Jetmalani 1969). This action appears to be due to the asparagamine, a polycyclic alkaloid (Sekine et al 1994).

Galactagogue

Galactagogue activity has been demonstrated in animal models (Patel & Kanitkar 1969, Sabnis et al 1968). One study of weaning rats found shatavari treatment increased the weight of mammary glands, inhibited involution of lobulo-alveolar tissue and maintained milk secretion (Sabnis et al 1968). It has been proposed that this effect may be due to the action of released corticoids and prolactin (Goyal et al 2003).

A randomised placebo-controlled trial of 64 lactating women in India found a herbal combination galactagogue formula (including shatavari 15%) had no effect on prolactin levels or lactation (Sharma et al 1996). Results were comparable for both treatment and placebo groups with prolactin levels declining after therapy; a similar frequency and volume of supplementary milk feeds; and similar weight gain in infants. Drop out rates were high (17.2%) and the majority of women were using supplemental feeding, which may have affected the results, however results remained comparable when stratified for exclusive and non-exclusive breast feeding. Since shatavari was only one component of the formula, it is possible that the treatment dose was too low to have an effect and further clinical trials are required using singular treatment with shatavari.

Antidiarrhoeal

Ethanol and aqueous extracts (200 mg/kg) of shatavari root have been shown to inhibit castor oil induced diarrhoea, and PGE_2 induced enteropooling (excessive secretion of water and electrolytes); and reduced gastrointestinal motility in rats (Venkatesan et al 2005). The anti-diarrhoeal activity described is similar to the drug loperamide.

Antioxidant

A. racemosus contains known antioxidant compounds including ascorbic acid, polyphenols and flavonoids (Visavadiya & Narasimhacharya 2005). Antioxidant properties have also been identified for racemofuran, asparagamine A and racemosol (Wiboonpun et al 2004). In vitro experiments have demonstrated antioxidant effects comparable to that of glutathione and ascorbic acid in inhibiting lipid peroxidation and protein oxidation (Kamat et al 2000). Animal models confirmed the inhibition of lipid peroxidation and also showed an increase in antioxidant enzymes (superoxide dismutase, catalase) and ascorbic acid (Bhatnagar et al 2005, Visavadiya & Narasimhacharya 2005).

Cardiovascular effects

Studies using different animal models indicate various effects on heart function. Goyal et al (2003) found lower doses of shatavari root produce a positive inotropic and chronotropic effect on frog's heart, with higher doses causing cardiac arrest. The extract was also found to produce hypotension in cats (attenuated by atropine) indicating a cholinergic mechanism; and a slight increase in bleeding time in rabbits (Goyal et al 2003).

Animal studies have also demonstrated that shatavari root powder added to the feed (at a rate of 5 and 10%) provided to hypercholesterolaemic rats significantly reduced the plasma and hepatic lipid (cholesterol) levels in a dose dependent manner and also decreased hepatic lipid peroxidation (Visavadiya & Narasimhacharya 2005). This effect was likely due to decreased absorption of exogenous cholesterol and increased conversion of endogenous cholesterol to bile acids for excretion. However, these doses may not be feasible in human studies.

Hepatoprotective

An alcoholic extract of shatavari root significantly reduces elevated levels of alanine transaminase (ALT), aspartate transaminase (AST) and alkaline phosphatase (ALP) in vivo (Muruganandan et al 2000).

Neuroprotective

Oxidative stress and excitotoxicity are considered to be major mechanisms of neuronal cell death in neurodegenerative disorders such as Alzheimer's and Parkinson's diseases. Experimental studies have demonstrated that shatavari extract may attenuate oxidative damage, elevating glutathione peroxidase (GPx) activity and glutathione (GSH) content; and could result in a protective effect on kainic acid (KA)-induced excitotoxicity (Parihar & Hemnani 2004).

Antidepressant

Antidepressant activity has been demonstrated in vivo. A methanolic extract of *A. racemosus* root (MAR) (standardised to saponins 62.2% w/w) was given to rats in doses of 100, 200 and 400 mg/kg daily for 7 days. The results show that MAR decreased immobility in forced swim tests (FST) and increased avoidance response in learned helplessness tests (LH), indicating antidepressant activity. Effects were thought to be mediated through the serotonergic and noradrenergic systems, and augmentation of antioxidant defenses (Singh et al 2008).

Antineoplastic

An extract of shatavari root has been reported to reduce the incidence of DMBA (7,12-dimethyl benz(a)anthracene)-induced mammary cancer in

female rats (Rao 1981). The effect is thought to be due to properties that render the mammary epithelium refractory to the carcinogen. Clinical implications remain to be tested.

Antilithic

An ethanolic extract of shatavari inhibited experimentally induced urinary lithiasis (stone formation) in vivo (Christina et al 2005). Administration of shatavari reduced elevated urinary concentrations of calcium, oxalate and phosphate, which contribute to stone formation, and increased urinary concentration of magnesium, which is thought to be protective. Elevated serum creatinine was also reduced.

Antitussive

Strong antitussive activity has been demonstrated in animal models. A methanolic extract of shatavari root (200 and 400 mg/kg orally) showed significant antitussive activity on sulfur dioxide-induced cough in mice. The dose dependent cough inhibition (40.0 and 58.5%, respectively) was comparable to that of 10–20 mg/kg codeine phosphate (36.0 and 55.4%, respectively) (Mandal et al 2000a).

CLINICAL USE

Shatavari has not been subjected to extensive clinical testing so most information is derived from traditional use and in vivo experiments.

Stress

Currently, evidence to support the use of shatavari as a sole agent for reducing the deleterious effects of stress on the body is limited. Animal studies using polyherbal formulations such as EuMil (Bhattacharya et al 2002, Muruganandam et al 2002) and Siotone (Bhattacharya et al 2000) have shown some promise, but further research is required.

Dyspepsia

Shatavari root is used in Ayurvedic medicine for the treatment of dyspepsia. This may in part be due to improved digestion via increased levels of amylase and lipase (Dange et al 1969), and its ability to promote gastric emptying in a manner comparable to metoclopramide (Goyal et al 2003), and to normalise intestinal hypermotility (Rege et al 1999).

Gastrointestinal ulcers

In animal models, shatavari has been shown to reduce the incidence and increase the rate of healing of ulcers; while also relieving the pain and burning associated with duodenal ulceration (Goyal et al 2003). Antiulcerogenic activity of a crude extract of shatavari (100 mg/kg/day orally) has been found to be comparable to a standard antiulcer drug ranitidine (30 mg/kg/day orally) in rats. The effect may be related to an inhibition of hydrochloric acid and protection of the gastric mucosa (Bhatnagar & Sisodia 2006).

Prevention of infection

In vitro and animal experiments have demonstrated positive effects on immunity (particularly on the activity of macrophages) (Rege et al 1989, Rege & Dahanukar 1993) as well as antibacterial effects against *Escherichia coli*, *Shigella dysenteriae*, *Shigella sonnei*, *Shigella flexneri*, *Vibrio cholerae*, *Salmonella typhi*, *Salmonella typhimurium*, *Pseudomonas putida*, *Bacillus subtilis* and *Staphylococcus aureus* (Mandal et al 2000b). Further research is required in clinical trials to ascertain whether these effects can be demonstrated in humans.

OTHER USES

Hormonal disturbances in women

Traditionally shatavari is used as a 'rejuvenative tonic' for females and for lowered libido and infertility in both sexes. Due to its oestrogenic effects it is often used by herbalists for the treatment of conditions related to low oestrogen including some presentations of PMS and menopause; and to re-establish normal ovulation and menstruation patterns (Trickey 2003). Human trials have demonstrated positive results for dysfunctional uterine bleeding, dysmenorrhoea, PMS and menopausal symptoms, however these studies used the polyherbal formulations EveCare® and Menosan which contain *A. racemosus* (Bopana & Saxena 2007) so it is difficult to ascertain the role played by shatavari alone.

Promoting lactation

Shatavari root is used traditionally in Ayurvedic medicine to increase milk production and secretion during lactation. Early animal studies support this use (Sabnis et al 1968, Patel & Kanitkar 1969), however only one clinical trial has been conducted involving a polyherbal formulation containing shatavari (15%) which failed to find a significant effect (Sharma et al 1996).

Polyherbal combinations including *A. racemosus* have shown more promise. Ricalex (Aphali Pharmaceutical Ltd, Ahmednagar) (Joglekar et al 1967) and Lactare (TIK Pharma, Chennai) have been shown to increase milk production in women complaining of deficient milk secretion (Goyal et al 2003). However, it would appear that this effect may be due to other herbs contained in the formulas or to a synergistic interaction between the herbs, rather than the effect of shatavari alone.

Diarrhoea

Shatavari root is used traditionally in Ayurvedic medicine for the treatment of diarrhoea and dysentery. Ethanol and aqueous extracts of shatavari root demonstrate effects similar to loperamide by inhibiting diarrhoea, enteropooling and gastrointestinal motility (Venkatesan et al 2005). Human studies are warranted to confirm these effects.

DOSAGE RANGE

Fluid extract (1:2): 30–60 mL/week (Australian manufacturer's recommendations).

ADVERSE REACTIONS

No significant adverse events or biochemical liver dysfunction was noted in a randomised controlled trial of shatavari (Sharma et al 1996). Due to the saponin content, gastric irritation may occur in some individuals.

SIGNIFICANT INTERACTIONS

As controlled studies are not available, interactions are currently speculative and based on evidence of pharmacological activity. No evidence could be located that suggested any negative drug interactions.

Metoclopramide

As shatavari root was found in animal studies to have similar effects on gastric emptying time to the antiemetic drug metoclopramide (a synthetic dopamine antagonist), an additive effect is possible (Dalvi et al 1990).

Diphtheria, tetanus, pertussis (DTP) vaccine

Experimental studies have suggested a possible immunoadjuvant effect in animals immunised with diphtheria, tetanus, pertussis (DTP) vaccine, increasing antibody titres to *Bordetella pertussis* and providing improved immunoprotection on challenge (Gautam et al 2004). Beneficial effects possible.

CONTRAINDICATIONS AND PRECAUTIONS

No toxic effects or mortality have been observed with doses ranging from 50 mg/kg to 1 g/kg for 4 weeks, and acute and subacute (15–30 day) toxicity studies have not detected any changes in results of vital organ function tests. The LD50 is >1 g/kg (Rege et al 1999).

As inhibition of hydrochloric acid has been proposed as a possible factor contributing to the antiulcer effects of shatavari (Bhatnagar & Sisodia 2006), those with hypochlorhydria may need to be observed.

Herbs with theoretical oestrogenic effects may not be suitable for those with or at risk of oestrogen dependent tumours. The clinical significance however is unclear.

The Commission E has approved the use of *A. officinalis* root in irrigation therapy for inflammatory diseases of the urinary tract and for prevention of kidney stones, however this should be avoided if oedema exists due to functional heart or kidney disorders (Blumenthal et al 2000). Similar cautions might be expected for *A. racemosus*.

PREGNANCY USE

Although shatavari has been used traditionally to promote conception and for threatened miscarriage, teratogenicity has recently been demonstrated in rats at doses of 100 mg/kg/day for 60 days (Goel et al 2006). Caution should be exercised in pregnancy until more is known about effects in humans. While the traditional use of shatavari in breast feeding has not been supported by human studies (Sharma et al 1996), no significant side effects were reported in clinical trials.

PATIENTS' FAQs

What will this herb do for me?

It is difficult to determine what effects shatavari will display when used as a sole treatment, as it is most often tested as part of a polyherbal combination formula. The herbal combinations containing shatavari have a myriad of uses, such as improving digestion, promoting lactation and increasing libido. Shatavari root is used traditionally in Ayurvedic medicine for the treatment of diarrhoea and dysentery, gastric ulcers and dyspepsia, threatened miscarriage and as a galactogogue.

When will it start to work?

This is difficult to estimate as the majority of human trials have been conducted with polyherbal preparations containing shatavari and not with shatavari as a sole treatment.

Are there any safety issues?

Caution should be exercised in pregnancy until more is known about the potential teratogenic effects.

PRACTICE POINTS/PATIENT COUNSELLING

- In Ayurvedic medicine shatavari is used in approximately 64 Ayurvedic polyherbal formulations. As much of the current research focuses on these preparations it is difficult to ascertain the pharmacological and clinical effects of the individual herb.
- Shatavari may exert beneficial effects on digestion by increasing levels of lipase and amylase, promoting gastric emptying, normalising intestinal motility and protecting against ulceration.
- Shatavari is used, often in combination with other herbs, to improve milk production in lactating women, although human data supporting this effect are currently lacking.
- Animal models suggest that the steroidal saponins contained in *A. racemosus* may exert some hormonal effects which may account for its reputation as a female tonic and aphrodisiac.
- As teratogenicity has recently been demonstrated in rats, caution should be exercised in pregnancy until more is known about effects in humans.
- Demand for shatavari in combination with destructive harvesting techniques and deforestation has resulted in the plant becoming 'endangered' in its natural habitat.

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Slippery elm

HISTORICAL NOTE The dried inner bark of the slippery elm tree was a popular remedy used by many Native American tribes, and subsequently taken up by European settlers. It was mixed with water and applied topically to treat wounds, bruises and skin irritations, and used internally for sore throat, coughs and gastrointestinal conditions. When mixed with milk, it was used as a nutritious gruel for children and convalescents. It also gained a reputation as an effective wound healer among soldiers during the American Civil War. From 1820 until 1960, it was listed in the US Pharmacopeia as a demulcent, emollient and antitussive (Ulbricht & Basch 2005). The name 'slippery elm' refers to the slippery consistency of the inner bark when it comes into contact with water.

COMMON NAME
Slippery elm

OTHER NAMES
American elm, Indian elm, moose elm, red elm, sweet elm, winged elm

BOTANICAL NAME/FAMILY
Ulmus fulvus or *Ulmus rubra* (family Ulmaceae)

According to current botanical nomenclature, it should now be referred to as *Ulmus rubra*.

PLANT PART USED
Dried inner bark

CHEMICAL COMPONENTS
The inner bark chiefly contains mucilage (various hexoses, pentoses, methylpentoses), glucose, polyuronides, tannins, galacturonic acid, L-rhamnose, D-galactose, starches, fat, phytosterols, sesquiterpenes and cholesterol (Beveridge et al 1969, Duke 2003, IM Gateway Database 2003, Newell et al 1996). The bark provides 2740 kilocalories

Clinical note — Mucilages
Mucilages are hydrophilic structures, capable of trapping water, which causes them to swell in size and develop a gel-like consistency. The gels tend to have soothing properties and can be broken down by bowel flora when taken internally (Mills & Bone 2000). Mucilages are known to have beneficial effects on burns, wounds and ulcers when applied externally and on gastric inflammation, irritations and diarrhoea when taken internally.

per kilogram. It contains a variety of nutritional factors such as glucose, calcium, iron, vitamin C, thiamine, zinc, magnesium and potassium, providing support for its traditional use as a nutritious gruel.

MAIN ACTIONS

The pharmacological actions of slippery elm have not been significantly investigated in clinical studies. Therefore, information is generally based on what is known about key constituents found within the herb.

Soothes irritated and inflamed tissue

The large amount of mucilage found in slippery elm bark will coat the surface of mucous membranes or wounds and sores when it comes in contact with water, and form a gel-like layer. Laboratory research has shown that mucilaginous medicinal plants, such as slippery elm, can decrease local irritation in acute gastritis.

Nutritive demulcent

A number of constituents, such as starch, glucose, calcium, iron, vitamin C, thiamine, zinc, magnesium and potassium are present in slippery elm, making it a source of many nutritional factors (Duke 2003).

Antioxidant

In vitro studies show a free radical scavenging activity that may relate to its anti-inflammatory action (Langmead et al 2002).

CLINICAL USE

The therapeutic effectiveness of slippery elm has not been significantly investigated under clinical trial conditions, so evidence is derived from traditional, in vitro and animal studies.

Gastrointestinal conditions

Based on traditional evidence, slippery elm is taken internally to relieve the symptoms of gastritis, acid dyspepsia, gastric reflux, peptic ulcers, irritable bowel syndrome and Crohn's disease.

It is widely accepted that the mucilage acts as a barrier against the damaging effects of stomach acid on the oesophagus and may also exert mild anti-inflammatory activity locally. Currently, clinical research is not available to determine the effectiveness of slippery elm in these conditions; however, anecdotally the treatment appears to be very successful and patients report rapid improvement in upper gastrointestinal symptoms.

Clinical note — Essiac tea
Slippery elm is one of the key ingredients in Essiac tea, which was reportedly developed by the Ojibwa tribe of Canada and named after an Ontario nurse (Rene Caisse) to whom the formula for the herbal tea was given by an Ojibwa healer in 1922 (Smith & Boon 1999). It is used to treat a variety of diverse conditions, such as allergies, hypertension and osteoporosis. The tea is made up of a mixture of four herbs, *Arctium lappa* (burdock root), *Rumex acetosella* (sheep sorrel), *Ulmus rubra* (slippery elm) and *Rheum officinale* (rhubarb) and is considered to possess antioxidant and, possibly, anticancer activities (Leonard et al 2006). As a result, it is used widely by North American cancer patients during chemo- and radiotherapies (Cheung et al 2005) for reduction in symptoms associated with cancer treatment and as a possible adjunctive treatment. In vitro tests with Essiac have identified anticancer activity, although its effects in vivo are controversial and evidence of efficacy is anecdotal (Leonard et al 2006). A recent study demonstrated that Essiac tea effectively scavenges several types of radicals and possesses DNA-protective effects (Leonard et al 2006). A retrospective cohort study of 510 women with breast cancer found that Essiac did not improve quality-of-life scores or mood (Zick et al 2006). Daily doses of Essiac ranged from 12 to 114 mL with the average dose being 43.6 mL, corresponding to doses recommended on popular products. Duration of treatment ranged from 1 to 28 months, with the average being 11.1 months. The formula was well tolerated with only 2 women reporting minor adverse events, whilst many women reported beneficial effects.

Solid dose tablets and capsules are used in the treatment of diarrhoea when it is believed the fibre will slow down gastric transit time and act as a bulking agent. Although clinical studies are not available to determine its effectiveness, the high mucilaginous content and presence of tannins in the herb provide a theoretical basis for its use.

Dermatitis and wounds

Slippery elm has also been used as a topical agent to soothe irritated and/or inflamed skin conditions, wounds and burns and to draw out boils and abscesses (Fisher & Painter 1996). When applied, it forms a protective gel-like layer, which is considered to have soothing properties.

OTHER USES

Traditionally, slippery elm is used to treat bronchitis, cystitis and intestinal parasites. Externally, it has been used to treat gout, inflamed joints and toothache (Fisher & Painter 1996).

DOSAGE RANGE

Owing to insufficient data available from clinical studies, doses have been derived from Australian manufacturers' recommendations.

Gastrointestinal symptoms

- One to two capsules containing 150 mg of slippery elm before meals.
- Fluid extract (60%): 5 mL three times daily.
- Half a teaspoon of slippery elm bark powder is mixed with one cup of hot water and taken up to three times daily. For added flavouring, cinnamon or nutmeg can be added.

External use

- Mix the coarse powdered bark with enough boiling water to make a paste and use as a poultice (Hoffman 1983).

TOXICITY

Insufficient reliable information is available.

ADVERSE REACTIONS

Insufficient reliable information is available.

SIGNIFICANT INTERACTIONS

Controlled studies are unavailable, but interactions are theoretically possible with some medicines.

Since slippery elm forms an inert barrier over the gastrointestinal lining, it may theoretically alter the rate and/or extent of absorption of medicines with a narrow therapeutic range (e.g. barbiturates, digoxin, lithium, phenytoin, warfarin). The clinical significance of this is unclear. Separate doses by 2 h.

CONTRAINDICATIONS AND PRECAUTIONS

Insufficient reliable information is available.

PREGNANCY USE

It is likely to be safe, but safety is still to be established.

PATIENTS' FAQs

What will this herb do for me?

The inner bark of slippery elm is highly mucilaginous, meaning that it forms a thick gel-like substance when combined with water. Traditionally, it has been used internally to relieve symptoms of dyspepsia and inflamed bowel conditions and topically to soothe irritated skin and promote wound healing.

When will it start to work?

Whether used internally for upper gastrointestinal symptoms (such as reflux and dyspepsia) or applied topically to irritated skin, it should theoretically provide quick symptomatic relief; however, research to confirm this is not available.

Are there any safety issues?

Although slippery elm has not been scientifically investigated, the Federal drug agency (FDA) in the USA has approved it as a safe demulcent substance.

PRACTICE POINTS/PATIENT COUNSELLING

- Slippery elm inner bark is a highly mucilaginous substance, which has been traditionally used as a topical application to soothe irritated and inflamed skin conditions and promote wound healing.
- It is used internally to soothe an irritated throat and is often combined with antiseptic herbs.
- Slippery elm is used to provide symptomatic relief in acid dyspepsia, gastrointestinal reflux and inflammatory bowel diseases, but has not been scientifically studied to any significant extent.
- Overall, slippery elm has not been significantly investigated in clinical studies, so most information is derived from traditional sources.

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Soy

HISTORICAL NOTE Soybeans were one of the first crops grown by humans and have been consumed for approximately 5000 years in China where they are regarded as both a food and a medicine. During the Chou dynasty 1134–246 BC fermentation techniques were developed to produce tempeh, miso and tamari soy sauce, with tofu being invented around the second century BC. Soy first reached the West as imported soy sauce, and soybean cultivation began in the 1770s, primarily for animal feed. It was not until World War I that soy became a significant crop for human consumption (Natural Standard Patient Monograph 2005). Soy protein was first produced in the 1930s for its functional properties and used as a pigment binder for paper, a foam for fire extinguishers and a fibre for making artificial silk before being used as a food supplement in the 1960s.

COMMON NAME
Glycine max

OTHER NAMES
Glycine soja, dolichos soja, glycine gracilis, glycine hispida, phaseolus max, soja hispida, soja max

BOTANICAL NAME/FAMILY
Glycine max (family Fabaceae [Leguminosae])

PLANT PART USED
Bean

CHEMICAL COMPONENTS
Soybeans are a high-nutrient food containing up to 50% protein. Soy protein contains all of the essential amino acids in sufficient quantities to act as a sole protein source with methionine (a precursor of homocysteine) being the limiting amino acid (Young 1991).

Soy is a major food source of phyto-oestrogens (isoflavones and lignans), with each gram of soy protein containing approximately 1–3 mg of isoflavones, including glycosides of genistein, daidzein and glycitein (Erdman 2000). Soy also contains the lignans secoisolariciresinol, matairesinol, syringaresinol, lariciresinol, isolariciresinol and pinoresinol (Penalvo et al 2004), as well as soy lecithin (a phospholipid containing linoleic and linolenic acid), vitamin E (in its four isomeric forms as alpha, beta, gamma and delta-tocopherol), oligosaccharides, the phytosterols beta-sitosterol, campesterol and stigmasterol, phytates and protease inhibitors, inositol hexaphosphate, saponins and oligosaccharides (Mazur et al 1998, Tripathi & Misra 2005).

MAIN ACTIONS
Daidzein, an isoflavone found in soy, is metabolised to the more metabolically active equol and O-desmethylangolensin (O-DMA) by as yet unspecified intestinal bacteria. Following soy or daidzein consumption, approximately 30–50% of the human population produce equol, and approximately 80–90% produce O-DMA; however, the significance of this is uncertain, despite some studies suggesting that the ability to produce equol and O-DMA may be associated with reduced risk of certain diseases, including breast and prostate cancers (Atkinson et al 2005).

Predicting the effects of isoflavones in vivo is difficult because the route of administration, chemical form of the phyto-oestrogen, its metabolism, bioavailability, half-life, timing and level of exposure, intrinsic oestrogenic state and non-hormonal secondary mediated actions of isoflavones may all influence their biological and clinical effects (Setchell & Cassidy 1999) and the mechanisms for the clinical effects of soy are yet to be fully evaluated (Balk et al 2005, Setchell & Cassidy 1999).

Oestrogen receptor/hormonal modulation
Soy isoflavones and lignans share structural similarities with oestrogen and are referred to as phyto-oestrogens and/or selective oestrogen receptor modulators (Sliva 2005). Soy isoflavones have weak oestrogenic activity. The order of activity in in vivo assays is glycitein > genistein > daidzein (PDRHealth 2004). Soy isoflavone glycosides bind weakly to both oestrogen receptors, with the binding affinity of genistein, dihydrogenistein and equol being comparable to the binding affinity of 17-beta-oestradiol (Morito et al 2001).

Isoflavones have complex actions that may be tissue specific and may act as partial oestrogen agonists and antagonists, as well as having non-classical effects on plasma membranes and cell signalling pathways (Setchell & Cassidy 1999).

The oestrogenic effects of soy are postulated to contribute to protective effects against cardiovascular disease, cancer and menopausal symptoms. Although a review of 861 studies on the effects of phyto-oestrogens suggests that they are indeed biologically active in humans (Knight & Eden 1996), major gaps in knowledge still exist regarding the effects of phyto-oestrogen supplements on bone diseases, various cancers, menopausal symptoms and cognitive function (Lu et al 2001, Stark & Madar 2002). Interestingly, soy has a greater affinity for the oestrogen beta-receptor than the alpha-receptor. The beta-receptor is found in brain, bone, bladder and vascular epithelia, tissues in which isoflavones purportedly have activity (Setchell & Cassidy 1999).

Genistein has been found to have an oestrogen-like effect on the serum lipid profile (Yildiz et al 2005); however, in a double-blind, placebo-controlled trial in 40 healthy postmenopausal women aged 50–75 years, 40 g of soy protein containing 118 mg isoflavones did not produce biologically significant oestrogenic effects on coagulation, fibrinolysis or endothelial function (Teede et al 2005). In another 12-month, double-blind, randomised trial of soy protein containing 99 mg isoflavones/day in 202 postmenopausal women, systolic blood pressure (SBP) and diastolic blood pressure (DBP) decreased and endothelial function improved in the equol producers, with increased blood pressure and deterioration in endothelial function seen in the equol non-producers (Kreijkamp-Kaspers et al 2005).

A review of 50 RCTs of soy and endocrine function suggest that there are no consistent statistically significant effects of soy on follicle stimulating hormone (FSH) or thyroid stimulating hormone (TSH) levels or on oestradiol levels at the follicular phase, or on menstrual cycle length.

Hormonal effects in men
Whether soy products have a significant effect on testosterone levels in healthy males remains uncertain (Balk et al 2005); however, the results of two trials suggest it may. One study found that soy protein powder decreases serum testosterone levels in healthy men and acts as an oestrogen receptor agonist (Goodin et al 2007) while another small study of 99 male partners of subfertile couples identified that a higher intake of soy foods and soy isoflavones was associated with a lower sperm concentration while being unrelated to sperm motility, sperm morphology or ejaculate volume (Chavarro et al 2008).

Cardiovascular disease

There are many potential mechanisms by which soy isoflavones may improve cardiovascular outcomes, including reduction in total cholesterol, LDL, HDL, triglycerides, lipoprotein A, blood pressure, C-reactive protein, homocysteine, endothelial function, systemic artery compliance and oxidised LDL (Balk et al 2005). Further mechanisms include an inhibition of pro-inflammatory cytokines, cell adhesion proteins and inducible nitric oxide production, potential reduction in the susceptibility of the LDL particle to oxidation, inhibition of platelet aggregation and an improvement in vascular reactivity (Rimbach et al 2008).

Consumption of soy protein may further produce cardiovascular benefits through multiple mechanisms, including the low methionine content reducing serum homocysteine concentration (Nagata et al 2003), reduction of the insulin/glucagon ratio (Sanchez & Hubbard 1991), down-regulation of the hepatic transcription factor sterol regulatory element binding protein-1, which in turn reduces lipotoxicity in the liver (Torres et al 2006), regulation of hepatic lipid metabolism through upregulation of LDL receptors and increase in bile acid secretion (Potter 1995), reducing hepatic fatty acid and triglyceride biosynthesis and increasing fatty acid oxidation (Tovar et al 2005), preventing the transfer of fatty acids to extra adipose tissues by increasing the adipocyte hormone adiponectin (Nagasawa et al 2003), and increasing bile acid secretion and bacterial conversion of cholesterol to the non-absorbable coprostanol (Huff & Carroll 1980). Soy protein peptides may also act to decrease intestinal cholesterol absorption and bile acid uptake, reduce aortic accumulation of cholesterol esters and suppress food intake and gastric emptying by increasing cholecystokinin, and inhibiting angiotensin-converting enzyme (Torres et al 2006). An RCT, however, suggests that decreasing vascular inflammation and homocysteine concentration are unlikely to be mechanisms by which soy consumption reduces coronary heart disease risk (Greany et al 2008).

A review by the North American Menopause Society suggests that the most convincing health effects of soy can be attributed to the actions of isoflavones on lipids, with studies finding statistically significant reductions in LDL and triglycerides, as well as increases in HDL (Greenwood et al 2000). This is supported by many epidemiological studies reporting an association between a high intake of soy isoflavones and reduced cardiovascular risk (Kokubo et al 2007). Further support comes from clinical trials with a recent meta-analysis of 11 studies reporting that soy isoflavones significantly reduced serum total and LDL cholesterol but did not change HDL cholesterol and triglycerides and that soy protein containing enriched or depleted isoflavones also significantly improved lipid profiles with reductions in LDL cholesterol being larger in hypercholesterolaemic than in normocholesterolaemic subjects (Taku et al 2007). Furthermore, recent evidence indicates that soy consumption may improve glycaemic control and cardiovascular risk markers in postmenopausal women (Atteritano et al 2007, Azadbakht et al 2007).

It is unclear how soy exerts its beneficial effects on lipid metabolism or exactly which components are most active. It is suspected that these include soy protein, bioactive peptides, interaction of isoflavones within the intact soy matrix or other compounds (Cassidy & Hooper 2006, Torres et al 2006). It is reported that isolated soy protein that maintains the native protein structure is more effective in reducing serum lipids than denatured protein (Hoie et al 2007). Soy protein is also reported to have beneficial effects on renal function, with suggestions that the isoflavones genistein and daidzein reduce glomerular damage by protecting LDL from oxidation and the high arginine content acts as a precursor for NO thus improving renal flow (Torres et al 2006).

Although it has been suggested that there is no evidence of beneficial effects of phyto-oestrogens on blood pressure, arterial compliance or oxidation of LDL cholesterol, there may be beneficial effects on endothelial function and homocysteine concentrations (Cassidy & Hooper 2006). This is supported by a study that reports that a greater isoflavone intake is associated with better vascular endothelial function and lower carotid atherosclerotic burden in people at high risk of cardiovascular events (Chan et al 2007). Soy supplementation has also been reported to improve endothelial function in renal transplant patients (Cupisti et al 2007). Soy isoflavones have, however, been found to improve systemic arterial compliance in perimenopausal and menopausal women (Nestel et al 1997). Soy protein, regardless of isoflavone content, modulates serum lipid ratios in a direction beneficial for cardiovascular disease risk in healthy young men (McVeigh et al 2006) and soy consumption is associated with decreased carotid intima-media thickness and plasma lipids with the association being stronger for men than women (Zhang et al 2008).

Anti-osteoporotic

There has been speculation that the oestrogenic effects of soy isoflavone may help prevent osteoporosis (Setchell & Cassidy 1999). A recent review of in vitro and in vivo studies suggests that soy protein prevents bone loss and that soy isoflavones stimulate the synthesis and the expression of alkaline phosphatases in osteoblasts, and food enriched with isoflavones prevented the reduction of bone mineral density (BMD) in ovariectomised rats or mice and inhibited excretion of urinary deoxypyridinoline (Horiuchi 2005). Animal studies have also found a synergy between soy isoflavones and supplemental calcium in improving BMD, particularly in the lumbar spine (Ward 2005).

In human trials, 35 g/day soy protein for 12 weeks was found to significantly reduce urinary deoxypyridinoline and increase total alkaline phosphatase in a small study of 15 women aged 45–64 years (Roudsari et al 2005); however, randomised trials in humans indicate that soy protein and soy isoflavones do not significantly affect calcium metabolism in postmenopausal women (Spence et al 2005)

or improve BMD (Horiuchi 2005), despite having an effect on markers of bone formation (Arjmandi et al 2005).

It has further been suggested that the beneficial effects of soy isoflavones on bone may be life-stage specific and dependent on the number of oestrogen receptors and the endogenous hormone milieu. Perimenopausal and early menopausal women may therefore be more receptive to the therapeutic effects of isoflavones on bone loss prior to the diminution of oestrogen receptors that occurs in the postmenopausal years (Reinwald & Weaver 2006).

Anticancer

To date there have been no positive human intervention studies and the evidence of soy's anticancer effects is based on epidemiological data, as well as in vitro and animal studies.

Soy phyto-oestrogens are converted by gut bacteria to derivatives with weak oestrogenic and antioxidative activities, and epidemiological studies suggest that the highest plasma levels of their metabolites are found in individuals living in countries or regions with low incidence of both cancer and cardiovascular disease (Mazur et al 1998). Although soy phyto-oestrogens have been implicated in soy's anticarcinogenic activity, a causal relation to disease prevention is hypothetical, as the exact mechanisms have not been elucidated (Adlercreutz 2002a, 2002b).

There are multiple mechanisms by which soy protein may protect against cancer, as there is evidence for soy isoflavones having oestrogenic, antioestrogenic, antioxidant, antiproliferative and antiangiogenic activities (Barnes et al 2000). Soy also contains other putative anticarcinogenic compounds such as lignans, saponins, phytates, protease inhibitors and phytosterols (Greenwood et al 2000) and it is possible that soy consumption may be a marker for other dietary factors.

It has been suggested that soy isoflavones may reduce breast cancer risk by affecting endogenous sex hormone concentrations and the menstrual cycle (Adlercreutz 2002a, 2002b, Setchell & Cassidy 1999) and that soy phyto-oestrogens may influence cancer growth through effects on oestrogen receptors, as well as through inhibition of tyrosine and other protein kinases, and other enzymes such as aromatase, alteration of growth factor activity and inhibition of angiogenesis (Adlercreutz 2002a, 2002b).

Genistein is the most studied of the phyto-oestrogens and has weak oestrogenic activity. It has also been found to cause apoptosis in cancer cells both in vitro and in vivo (Bylund et al 2000), stimulate several antioxidative enzymes, such as catalase, superoxide dismutase, glutathione peroxidase and reductase, induce tumour cell differentiation, downregulate the epidermal growth factor receptor and erbB2/Neu receptors in cancer cells, and also possibly inhibit tumour cell invasion by inhibiting MMP9 (92 kDa type IV collagenase) (Adlercreutz 2002a, 2002b). Genistein is also reported to inhibit angiogenesis, DNA topoisomerase II, protein tyrosine kinases, aromatase, NF-kappa-B and to downregulate TGF-beta and stimulate the sex hormone-binding globulin (PDRHealth 2004). Isoflavones have also been shown to inhibit the activity of aromatase (CYP19), thus decreasing oestrogen biosynthesis and producing antioestrogenic effects, which may be important in breast and prostate cancers (Moon et al 2006).

Soy isoflavones also demonstrate a variety of oestrogen-independent activities, and some of them are directly associated with the suppression of the invasive behaviour of breast cancer cells (Sliva 2005). Furthermore, it is suggested that variability in xenobiotic metabolising enzymes and the effect of flavonoid ingestion on enzyme activity may contribute to individual variations in susceptibility to diseases such as cancer (Moon et al 2006).

Although in vitro and animal models point to several pathways by which isoflavones may reduce incidence of cancer (Rosenberg Zand et al 2002), and experimental evidence also exists for an inhibitory effect of soy bran on prostate cancer growth and of isolated lignans on colon cancer (Adlercreutz 2002a, 2002b), clinical trial data supporting this are still lacking.

OTHER ACTIONS

Antioxidant

Oxygen stress is believed to contribute to menopause and degenerative changes associated with ageing and it is suggested that antioxidants, such as soy isoflavones, may help to protect mitochondria against premature oxidative damage (Miquel et al 2006). Although several clinical trials have suggested that soy intake decreases oxidative stress and that soy isoflavones, such as genistein, have antioxidant properties in vitro, results of supplementation in clinical trials are inconclusive. Furthermore, diets relatively high in soy protein or soy-derived isoflavones are reported to have little effect on plasma antioxidant capacity or biomarkers of oxidative stress (Vega-Lopez et al 2005). It has been suggested that genistein may be a potential therapy for multiple sclerosis as it has been observed to reduce experimental autoimmune encephalomyelitis in mouse models (De Paula et al 2008).

Cognitive function

Soy isoflavones may mimic the actions and functions of oestrogen on the brain, and they have been shown to have positive effects on the cognitive function in females, whereas results in males are inconsistent. Soy isoflavones, and particularly genistein, have been suggested to influence cognitive function via an oestrogen receptor-mediated pathway and via the inhibition of tyrosine kinase; however, definitive data are still lacking (Lee et al 2005).

CLINICAL USE

Soybeans are usually consumed as fermented and non-fermented soy foods such as tofu, miso and tempeh, as well as whole soybeans, soy nuts, soy milk or soy cheese, and soy flour is a common ingredient in foods, beverages and condiments (Sliva 2005). Wide variability has been reported in the total amount of isoflavones in commercial soy

products with levels being generally lower than the values on the product labels (Nurmi et al 2002).

Menopausal symptoms

The natural oestrogen receptor activity of soy is popularly considered an alternative to controversial hormone replacement therapy (HRT) for postmenopausal women (Sliva 2005). The results of numerous reviews and meta-analyses remain inconclusive. A recent Cochrane review of various phytooestrogens for vasomotor menopausal symptoms found a strong placebo effect in most trials and concluded there is no evidence of effectiveness in the alleviation of menopausal symptoms with the use of phytoestrogen treatments (Lethaby et al 2007). This is contrasted by a more specific review of 21 trials of soy and/or isoflavones on hot flushes and night sweats that suggests that, although results are inconsistent, most RCTs of isoflavone supplements found reductions in weekly hot flushes of between 7% and 40%; however, the quality of studies was generally low (Balk et al 2005). Another systematic review and meta-analysis that included 17 trials found that isoflavone supplementation significantly reduced flushes, with the percentage reduction being related to the number of baseline flushes per day and the dose of isoflavone studied (Howes et al 2006). A review that examined six systematic reviews and performed a meta-analyses of 25 randomised controlled trials (RCTs) assessing the use of phytoestrogens for the treatment of the climacteric syndrome found contradictory results with no statistically significant reduction of vasomotor symptoms for phyto-oestrogens (Tempfer et al 2007). Similarly a recent analysis of 17 trials found mixed results for the effects of soy isoflavone extracts on menopausal symptoms (Nelson et al 2006).

Theories explaining inconsistent results

Although some trial data seem to support the efficacy of isoflavones in reducing the incidence and severity of hot flushes, many studies have not found any difference between the isoflavone recipients and the controls (Greenwood et al 2000). These inconsistent results may be due to variations in the isoflavone content of the preparations used. A critical review of published studies stratified 11 studies according to genistein content and found the five studies that provided more than 15 mg of genistein all reported a statistically significant improvements in hot flushes while only one of the 6 studies that provided less than 15 mg of genistein reported any improvement (Williamson-Hughes et al 2006). In addition, confusion may arise from the fact that a variety of isoflavone sources have been tested, often without discriminating between the identities of individual isoflavones. The source of the isoflavones is not always stated which could be another important omission as bioavailability of active components could vary depending on the food matrix they are being presented in. As such, volunteers may be receiving greatly different doses or ranges of specific isoflavones from the different test products but researchers have not taken this into account when evaluating and comparing results. Finally, the composition and dose of soy supplements varies widely across studies, which makes comparisons and interpretations difficult (Low Dog 2005).

Cardiovascular disease

Substantial data from epidemiological surveys and nutritional interventions in humans and animals indicate that soy protein reduces serum total and LDL cholesterol and triglycerides, as well as hepatic cholesterol and triglycerides (Torres et al 2006). Based on this data, the US FDA has approved a food label health claim stating that a diet with a daily intake of 25 g of soy protein and low in saturated fat and cholesterol may reduce the risk of heart disease (Balk et al 2005). This claim, however, is only based on studies demonstrating beneficial effects on lipids and other biomarkers of risk, as there have been no published trials on the effects of soy on mortality or cardiovascular events (Cassidy & Hooper 2006). Furthermore, a review by the Nutrition Committee of the American Heart Association suggests that any reduction of serum lipids by soy protein is relatively small and that other benefits are not proven. As such soy supplementation is not recommended, despite acknowledgement that many soy products should be beneficial to cardiovascular and overall health because of their high content of polyunsaturated fats, fibre, vitamins, and minerals and low content of saturated fat (Sacks et al 2006).

Hypercholesterolaemia

At least six systematic reviews have assessed the effects of soy isoflavones on lipid levels, and suggest that a diet supplemented with soy protein isolate containing isoflavones reduces LDL cholesterol by approximately 0.15 mmol/L, but without clear effects on triglycerides or HDL cholesterol (Cassidy & Hooper 2006). In one of the systematic reviews that included a total of 68 RCTs, it is suggested that soy has small to moderate effects on lipids with significant reductions in total cholesterol (by 2.5%), LDL (3%), triglycerides (6%) and no significant change on HDL, and that the effect is independent of isoflavone content. This review further suggests that higher doses of soy protein are associated with greater LDL reduction in those with elevated baseline LDL levels (Balk et al 2005). A recent meta-analysis of 41 randomised controlled trials on isolated soy protein supplementation and serum lipids found similar results for total cholesterol, LDL and triglycerides but found that soy protein supplementation also resulted in a significant increase in HDL, with meta-regression analyses showing a dose–response relationship (Reynolds et al 2006). Similar results were reported in another meta-analysis of 23 RCTs published from 1995 to 2002. This study found that soy protein with isoflavones was associated with significant decreases in total cholesterol (by 3.8%), LDL (by 5.25%), and triglycerides (by 7.27%) and significant increases in serum HDL cholesterol (by 3.03%), with the observed changes being greater for those having higher baseline cholesterol levels or taking more than >80 mg/day isoflavone and the greatest lowering effects on total cholesterol and

LDL cholesterol occurred within short time frames, whereas improvements in HDL cholesterol were only observed in studies of longer than 12 weeks duration (Zhan & Ho 2005). A more recent meta-analysis on the effects of soy isoflavones without soy protein found that ingestion of 70 mg/day for 1–3 months does not improve total and LDL cholesterol levels in normocholesterolaemic menopausal women (Taku et al 2008).

Although many studies have reported that soy improves serum lipid levels, a critical analysis of investigations to date suggests that the effects are not impressive and questions the clinical importance of observed hypocholesterolaemic effects (Dewell et al 2006). More recent studies present inconsistent results. For example, one RCT found that a soy-based low-calorie diet significantly decreased serum total cholesterol and low-density lipoprotein cholesterol concentrations and had a greater effect on reducing body fat percentage than traditional low-calorie diets (Liao et al 2007) while another RCT suggests that regular consumption of foods providing 24 g soy protein/day from isoflavones had no significant effect on plasma LDL cholesterol in mildly hypercholesterolaemic subjects (Thorp et al 2008).

Blood pressure

In addition to beneficial effects on lipids, epidemiological data suggest that soy may affect blood pressure but this is not supported by clinical trial data. In an observational study of 45,694 participants of the Shanghai Women's Health Study, aged 40–70 years with no history of hypertension, diabetes or cardiovascular disease, the intake of soy foods over 2–3 years was inversely associated with both SBP and DBP, particularly among elderly women. Results of this study found that compared to women consuming less than 2.5 g/day of soy, consumption of more than 25 g/day was associated with a significant reduction in SBP of 1.9 mmHg and a significant reduction in DBP of 0.9 mmHg and that the inverse association between soy consumption and blood pressure became stronger with increasing age, with significant reductions of −4.9 mmHg for SBP and −2.2 mmHg for DBP in women aged over 60 years (Yang et al 2005).

Despite this epidemiological study, a recent systematic review evaluating all observation studies and clinical trials and subsequent meta-analysis found no reduction in blood pressure between patients treated with phyto-oestrogens and those on placebo (Rosero Arenas et al 2008). This is supported by a further review of 22 RCTs on the effect of soy consumption on blood pressure that found no discernible effect on either SBP or DBP (Balk et al 2005). The results of a recent RCT of low sodium soy sauce, however, suggests that the addition of soybean peptides to soy sauce results in a significant reduction in blood pressure in people with mild hypertension (Uchida et al 2008).

Cancer prevention

High levels of phyto-oestrogens (lignans and isoflavonoids) are frequently associated in epidemiological studies with low risk of breast, prostate and colon cancers, and breast cancer has been found to be associated with low lignan levels in the USA, Finland, Sweden and Australia.

In general, epidemiological studies have investigated the association between isoflavones and breast cancer risk by measuring dietary isoflavone intake, or levels of these in plasma/serum or urine, while some studies have looked at soy and breast cancer risk measuring exposure to soy-containing foods such as tofu and miso soup (Velentzis et al 2008). Two separate meta-analyses were conducted by Wu et al, which investigated the association in Western women and Asian women, accounting for the differences in dietary isoflavone intake (Wu et al 2008a). The results indicate that protective benefits are dose dependent. A meta-analysis of eight studies involving Asian women found that those consuming the highest amount (>20 mg/day) of dietary isoflavones had a 29% reduction in breast cancer risk when compared to low-level isoflavone intake (<5 mg/day). A moderate dose of 10 mg/day of isoflavones resulted in a 12% decrease in risk. In contrast, a meta-analysis of 11 studies carried out in women with Western diets found they consumed extremely low levels of isoflavones (median of highest intake was 0.8 mg/day and of lowest intake was 0.15 mg/day) and no association between isoflavone intake and breast cancer risk.

A meta-analysis of 21 studies found a significantly reduced incidence of breast cancer among past phyto-oestrogen users, while a review of 22 case-control and cohort studies that examined the incidence of breast cancer among women with and without a diet high in phyto-oestrogens found that none of the available RCTs document a protective effect of phytoestrogens for the clinical end points of breast cancer (Tempfer et al 2007). A meta-analysis of 18 epidemiological studies published from 1978 to 2004 that examined soy exposure and breast cancer risk concluded that high soy intake was modestly associated with reduced breast cancer risk with the association being stronger for premenopausal women (Trock et al 2006). This is supported by another review of the role of phyto-oestrogens, such as soy-containing isoflavones, for the prevention of breast cancer which concluded that a soy-containing diet in adult women is not or only slightly protective with regard to breast cancer, but may be beneficial if consumed in early life before puberty or during adolescence (Adlercreutz 2002a, 2002b).

Yet another meta-analysis of epidemiologic studies associating cancer risk with soy intake found statistically significant reductions in the mean overall risk estimate for breast (0.78), colon (0.70) and prostate (0.66) cancers for soy consumers (Badger et al 2005). This is supported by a study of over 35,000 Singapore Chinese women that found that 10 mg of isoflavones per day obtained in a standard serving of tofu had lasting benefits for the prevention of breast cancer in postmenopausal women (Wu et al 2008b). A further study suggests that the protective effect of soy differs by receptor status with reduced risk being evident in women who are oestrogen and progesterone receptor positive and HER2 receptor negative (Suzuki et al 2008). While

in vitro and rodent data have raised concerns that isoflavones may stimulate the growth of existing oestrogen-sensitive breast tumours, recent review suggests that there is little clinical evidence to suggest that isoflavones will increase breast cancer risk in healthy women or worsen the prognosis of breast cancer patients (Messina & Wood 2008).

A study of over 8300 Japanese men and women found no association between soy consumption and colon cancer (Akhter et al 2008).

Soy proteins, common in the Asian diet, have been shown to inhibit prostate cancer cell growth (Kurahashi et al 2008, Sonn et al 2005). In an epidemiological study of over 82,000 men legume intake was associated with a moderate reduction in prostate cancer risk that was deemed not to be due to isoflavones (Park et al 2008) while a case-controlled study suggests that isoflavones might be an effective dietary protective factor against prostate cancer in Japanese men (Nagata et al 2007). In RCTs in men aged 50–80 years, 12 months' supplementation with 83 mg/day isoflavones did not alter serum levels of prostate-specific antigen (PSA) in healthy men (Adams et al 2004), while 60 mg/day of soy isoflavone did alter serum PSA and free testosterone in some men with early stage prostate cancer (Kumar et al 2004). In another RCT involving 29 men with prostate cancer and scheduled to undergo a radical prostatectomy, supplementation with bread containing 50 g of soy grits was found to significantly reduce PSA levels (Dalais et al 2004).

Breast cancer survival

The role of soy isoflavone intake and the risk of breast cancer recurrence were investigated by Guha et al (2009). A cohort of 1954 Asian female breast cancer survivors was prospectively followed for 6.31 years and their dietary isoflavone intake was assessed on average 23 months postdiagnosis, using specific food frequency questionnaires (Guha et al 2009). Suggestive trends for a reduced risk of cancer recurrence were observed with increasing quintiles of daidzein and glycetin intake compared to no intake among postmenopausal women (*P* for trend: $P = 0.08$ for daidzein, $P = 0.06$ for glycetin) and among tamoxifen users ($P = 0.10$ for daidzein, $P = 0.05$ for glycetin). Among postmenopausal women treated with tamoxifen, there was an approximately 60% reduction in breast cancer recurrence comparing the highest to the lowest daidzein intakes (>1453 vs <7.7 microgram/day; HR, 0.48; 95% CI, 0.21–0.79, $P = 0.008$). Based on these findings, soy isoflavones consumed at levels comparable to those in Asian populations may reduce the risk of cancer recurrence in women receiving tamoxifen therapy and, importantly, does not appear to interfere with tamoxifen efficacy. Furthermore, it suggests that there is no evidence to indicate that soy foods are unsafe in breast cancer patients.

Two studies have explored prediagnosis phyto-oestrogen intake and breast cancer survival. One was conducted in the US and considered dietary intake of isoflavones in 1210 newly diagnosed pre- and postmenopausal breast cancer patients (Fink et al 2007). The highest quintile for consumption experienced a 48% lower risk of all-cause mortality compared with the lowest quintile of isoflavone intake. A similar reduction in risk was found for breast cancer mortality but it was limited to postmenopausal women.

In contrast, no association was found in Asian population according to a second study (Boyapati et al 2005). Dietary information gathered during a 5-year period prior to diagnosis was collected from 1459 Chinese breast cancer patients (both pre- and postmenopausal) finding no overall association between soy intake (either as total soy protein or as total isoflavone) prior to cancer diagnosis and disease-free breast cancer survival in the highest tertile of intake compared with those in the lowest tertile.

Clinical note — Soy and breast cancer patients

Whether soy and concentrated isoflavone sources confer beneficial or harmful effects in people with breast cancer has remained a controversial topic for some years.

The NSW Cancer Council supports the consumption of soy foods in the diet as part of the national dietary guidelines to eat a diet high in plant-based foods. A position statement released in 2006 states that the Cancer Council does **not** recommend or support the use of supplements such as soy protein isolates or isoflavone capsules for healthy men and women to prevent cancer and does not recommend or support the use of supplements for breast cancer survivors. There is evidence to suggest that women with existing breast cancer or past breast cancer should be cautious in consuming large quantities of soy foods or phyto-oestrogen supplements (Cancer Council 2009). Recent evidence indicates no harmful effects of including soy isoflavones consumed at levels comparable to those in Asian populations, and possibly benefits. In vivo studies suggest that the isoflavone daidzein may enhance the effect of tamoxifen against breast cancer burden and incidence. Whilst further research is required to confirm these findings, it appears that soy and isoflavone intake may not be as harmful as once thought.

Osteoporosis prevention

Isoflavone intervention has been found to significantly inhibit bone resorption and stimulates bone formation. A recent meta-analysis of 10 studies suggests that isoflavone intervention significantly attenuates bone loss of the spine in menopausal women (Ma et al 2008). Clinical data further suggest that effects become more significant when more than 90 mg/day of isoflavones are consumed (Ma et al 2008) while limited epidemiologic data among Asian populations generally suggests that lower amounts are efficacious (Messina et al 2004). The relationship between usual soy food consumption and fracture incidence was studied in 24,403 postmenopausal women aged 40–70 years who had no history of fracture or cancer in the Shanghai Women's Health Study. During a mean follow-up of 4.5 years, a statistically significant association

was found between soy or isoflavone consumption and fracture risk, with the association being more pronounced among women in early menopause (Zhang et al 2005).

A systematic review found 31 studies that evaluated the effect of soy on markers of bone health; however, few of these were long-term studies and they involved a wide variety of interventions making overall conclusions difficult. Of the five studies longer than 1 year, no consistent effect was seen on BMD or markers of bone formation (Balk et al 2005). Another systematic review that evaluated 15 clinical trials looking at the effects of isoflavones or isoflavone-rich soy protein on BMD suggests that isoflavones reduce bone loss in younger postmenopausal women (Messina et al 2004). A recent RCT has suggested that 24 months of treatment with genistein has positive effects on BMD in osteopenic postmenopausal women (Marini et al 2007) while another trial suggests that soy protein-containing isoflavones showed a modest benefit in preserving spine, but not hip BMD in older women (Newton et al 2006).

Cognitive function

A recent review of eight studies published in 2000–2007 found inconsistent outcomes with four of the seven studies conducted in postmenopausal women revealing a positive impact of isoflavones on cognitive function. The authors suggest that multiple factors such as variation in the composition of phytoestrogen interventions and the heterogeneous characteristics of the study population could have contributed to the discrepant results (Zhao & Brinton 2007).

OTHER USES

Soy infant formula

Soy has been used as an alternative for cow's milk in infant feeding for more than 30 years and may account for as much as 25% of infant formula (Mendez et al 2002). Soy formula is commonly used for infants with cow's milk allergy and there is evidence to suggest that soy milk may be effective in reducing infant colic (Garrison & Christakis 2000). There are few studies, however, examining the effects of phyto-oestrogens in infants. Although infants consuming soy formula may be exposed to 6–11 mg/kg/day of phyto-oestrogens and have plasma levels of isoflavones an order of magnitude higher than adults consuming soy foods (Setchell & Cassidy 1999), there is no obvious evidence to suggest any negative effects (Mendez et al 2002, Setchell & Cassidy 1999).

Diabetes and diabetic nephropathy

Replacing animal protein with soy protein has been found to improve various disease markers in patients with type 1 or type 2 diabetes and people with obesity. In a RCT of 104 patients with type 2 diabetes, 12 months of a soy-based meal replacement was found to significantly improve weight loss, HbA_{1c} and high-sensitivity C-reactive protein levels and significantly reduce the use of sulfonylureas and metformin compared to the use of individual diet plans (Li et al 2005). Another randomised trial involving 90 obese (non-diabetic) subjects suggests that 6 months on a low-fat, high-soy-protein diet can help to reduce fat while preserving muscle mass and improving glycaemic control and the lipid profile (Deibert et al 2004).

Soy protein supplementation is also reported to be of benefit in a number of pilot studies of diabetic nephropathy. In a controlled crossover trial, 8 weeks of substituting soy protein for animal protein significantly reduced glomerular filtration rates in 12 young adults with type 1 diabetes mellitus (Stephenson et al 2005). In another crossover trial, isolated soy protein significantly reduced urinary albumin and improved lipid profiles in 14 men with type 2 diabetes and nephropathy (Teixeira et al 2004). Similarly, improvement in lipid profile and renal function was observed in another randomised, crossover clinical trial of 14 patients with type 2 diabetes and nephropathy consuming a 35% soy protein and 30% vegetable protein diet for 7 weeks (Azadbakht et al 2003).

Seasonal allergic rhinitis

Polysaccharides from soy sauce have been shown to have anti-allergic activities in vitro and in vivo, and an 8-week double-blind study involving 51 subjects with seasonal allergic rhinitis found that oral supplementation with 600 mg of soy polysaccharides was effective in significantly improving symptom scores such as sneezing, nasal stuffiness and hindrance of daily life, as well as significantly improving the appearance and state of the nasal mucosa (Kobayashi 2005, Kobayashi et al 2005).

Premenstrual syndrome (PMS)

Isolated soy protein containing 68 mg/day (aglycone equivalents) soy isoflavones was found to significantly improve specific PMS symptoms, including headache, breast tenderness, cramps and swelling in a seven-menstrual cycle, double-blind, placebo-controlled, crossover intervention study in 23 women (Bryant et al 2005).

DOSAGE RANGE

Soy foods contain variable amounts of isoflavones. Soy flour contains 1.3 mg/g of isoflavones, with tofu containing 0.4 mg/g, soy milk 0.25 mg/g, tempeh 0.4 mg/g, miso 0.92 mg/g, soy sauce 0.023 mg/g, soybean paste 0.57 mg/g and soy cheese 0.05 mg/g (Coward et al 1993). Soy isoflavones are also available in some functional food products. Although soy oils and lecithin are used in many food ingredients, the typical Western diet provides negligible isoflavones, whereas Asian diets typically contain 20–50 mg of isoflavones (Nagata et al 1998). The optimal dose required to have clinical effects is yet to be established; however, the benefits seen in epidemiological studies are achieved with approximately 50 mg/day of isoflavones (Setchell & Cassidy 1999) and it is suggested that optimal soy protein and isoflavone intakes are 15–20 g/day and 50–90 mg/day, respectively with 25 g/day recommended for cholesterol reduction (Messina 2008).

TOXICITY

Soy and soy isoflavones are considered non-toxic in the doses that are generally consumed as foods. Soy may interfere with the absorption of synthetic thyroid hormone, and there is a theoretical concern based on in vitro and animal data that soy foods may increase risk of developing clinical hypothyroidism in individuals with compromised thyroid function and/or whose iodine intake is marginal (Messina & Redmond 2006). Soy food consumers should ensure their intake of iodine is adequate although studies suggest that soy isoflavones in a protein matrix do not significantly influence circulating thyroid hormones in healthy young men (Dillingham et al 2007).

Although the phyto-oestrogens may have hormonal activity, they have relatively short half-lives of approximately 6–8 h, which is contrasted with the environmental xeno-oestrogens that may persist for years in fat tissue and hence bio-accumulate (Setchell & Cassidy 1999).

ADVERSE REACTIONS

There is little suggestion of adverse effects of soy or isoflavones at physiological doses, although soy isoflavone supplements have induced gastrointestinal discomfort and menstrual complaints (Cassidy & Hooper 2006). Unconjugated soy isoflavones appear to be safe and well tolerated in healthy postmenopausal women at doses of 900 mg/day (Pop et al 2008).

Women with breast cancer (especially oestrogen-positive tumours) and men with prostate cancer should avoid the use of soy isoflavone supplements pending long-term safety studies. There is a case report of a 60-year-old man having gynaecomastia and breast tenderness along with high oestradiol levels due to soy milk consumption (Martinez & Lewi 2008).

There are structural similarities between birch pollen and soy allergens leading to allergic cross-reactions (Kleine-Tebbe et al 2008) and the potential for anaphylaxis (Jacquenet et al 2008).

SIGNIFICANT INTERACTIONS

Antibiotic administration blocks metabolism of isoflavones to equol through inhibition of the intestinal microflora, whereas a high carbohydrate milieu increases intestinal fermentation and results in more extensive biotransformation of phyto-oestrogens (Setchell & Cassidy 1999).

It has been suggested that isoflavones can inhibit the oxidative and conjugative metabolism of drugs in vitro and interact with transporters such as P-glycoprotein; however, their ability to interact with drugs remains uncertain until clinical studies can confirm these findings (Evans 2000).

Calcium, magnesium, zinc, copper and iron

Soy contains phytic acid, which may bind with certain minerals, such as calcium, magnesium, manganese, zinc, copper and iron, reducing their availability (PDRHealth 2004). Separate by 2–3 hours.

PRACTICE POINTS/PATIENT COUNSELLING

- Soy is a component of many foods and a nutritious source of protein.
- There are many different types and formulations of soy and people may react differently to soy products depending on their diet and the activity of their gut bacteria.
- In countries where people regularly consume soy products there appears to be lower incidence of cardiovascular disease, menopausal symptoms and some cancers.
- The most active agents in soy are the isoflavones, which are used to treat menopausal symptoms, and prevent osteoporosis, cancer and heart disease; however, their use is not yet based on large-scale clinical trials.
- The ability of soy to reduce menopausal symptoms is uncertain at present.
- Although there has not been much research on the use of soy in infants, there does not appear to be any adverse effects of feeding infants with soy formula.
- The long-term benefits of soy may relate to the lifetime exposure to the use of soy products.

Tamoxifen

Whilst the soy isoflavone genistein may theoretically compete with tamoxifen for oestrogen receptors, thereby reducing drug efficacy, a large prospective study found that soy isoflavones consumed at levels comparable to those in Asian populations may reduce the risk of cancer recurrence in women receiving tamoxifen therapy and, importantly, does not appear to interfere with tamoxifen efficacy. Furthermore, it suggests there is no evidence to indicate that soy foods are unsafe in breast cancer patients (Guha et al 2009).

Additionally, in vivo studies suggest that the isoflavone daidzein may enhance the effect of tamoxifen against breast cancer burden and incidence — possible beneficial effect under professional supervision. Usual dietary intake levels appear safe; however, the safety of concentrated extracts is yet to be established.

PREGNANCY USE

Soy is likely to be safe when used as a food; however, pregnant women and nursing mothers should avoid the use of soy isoflavone supplements pending long-term safety studies.

PATIENTS' FAQs

What will this supplement do for me?

Soy is a nutritious food and a good source of protein that appears to have beneficial effects on cholesterol, and possible activity against cancer, heart disease, osteoporosis and may positively affect cognitive function.

When will it start to work?

Clinical studies suggest the effects of soy take between 6 and 12 weeks to appear.

Are there any safety issues?

Soy is generally considered safe when taken as a food source or protein substitute; however, soy isoflavone supplements should be taken with caution in pregnancy, and in those with breast cancer or prostate cancer.

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Stinging nettle

HISTORICAL NOTE Stinging nettle has been used since ancient times, with Dioscorides and Galen in ancient Greece reporting diuretic and laxative effects for nettle leaf. It is also widely used for gynaecological complaints by North American Indians and in Ayurvedic medicine in India (Blumenthal et al 2000). The Latin root of *urtica* is *uro*, meaning 'I burn', indicative of the small stings caused by the hairs on the leaves of nettle when contact is made with the skin.

OTHER NAMES

Common nettle, brenessel, brennesselkraut, brennesselwurzel, urtica ortie, great stinging nettle, haarnesselkraut, haarnesselwurzel.

BOTANICAL NAME/FAMILY

Urtica dioica (family Urticaceae)

PLANT PARTS USED

Aerial parts and root.

CHEMICAL COMPONENTS

Constituents found within the leaf include vitamins A and C, beta-carotene, calcium and potassium, phosphorus, chlorophyll, magnesium and tannins, flavonoids, sterols and amines (US Department of Agriculture 2003).

Constituents found chiefly in the root include polysaccharides, lectins, lignans, fatty acids, terpenes and coumarin (Ernst et al 2001).

MAIN ACTIONS

Anti-inflammatory and analgesic

In vitro studies have identified anti-inflammatory activity for *Urtica* extract (Obertreis et al 1996a, 1996b, Riehemann et al 1999). The mechanism of action has not been fully elucidated, but test tube studies have demonstrated inhibitory effects on NF-kappa B activation and partial inhibitory effects on cyclo-oxygenase and 5-lipoxygenase derived reactions. Additionally, isolated phenolic acid from nettle has been shown to inhibit leukotriene B4 synthesis in a concentration-dependent manner in vitro.

Although extensive investigation has not been conducted in humans to confirm anti-inflammatory mechanisms, one study of 20 volunteers showed that oral ingestion of 1.34 g nettle extract for 3 weeks significantly decreased lipopolysaccharide-stimulated tumor necrosis factor-alpha (TNF-alpha) and interleukin-1 beta (IL-1-beta) when tested ex vivo but had no effects on cytokine levels (Teucher et al 1996).

In vitro data have shown that nettle leaf extract (IDS 30) reduces the induction of primary T-cell responses and TNF-alpha in T-cell mediated diseases such as rheumatoid arthritis (Broer & Behnke 2002). Faecal IL-1-beta and TNF-alpha concentrations were significantly reduced in mice with induced Crohn's disease treated with IDS 30 (Konrad et al 2005). Mice treated with nettle extract displayed less histological changes and general disease symptoms. The authors conclude that the effect may be due to a decrease in TH1 response and may constitute a new treatment option for prolonging remission in inflammatory bowel disease.

Hypotensive and diuretic

When administered intravenously to test animals, *Urtica* extract exerts an acute hypotensive action accompanied by diuretic and natriuretic effects (Tahri et al 2000). It is uncertain whether the same effects are seen with oral administration.

A review of in vitro and in vivo studies concluded that the hypotensive action of *U. dioica* is due in part to negative inotropic activity and a vasodilatory effect (Testai et al 2002).

Antihyperglycaemic

A 33% reduction in blood glucose was noted in rats administered 250 mg/kg of nettle leaf extract orally, 30 min before glucose loading (Bnouham et al 2003). Nettle was shown to decrease glucose absorption in the small intestine of rats under anaesthesia; however, administration of 500 mg/kg failed to modify blood glucose levels in alloxan-induced diabetic rats.

A sixfold increase in blood insulin levels occurred after intravenous administration of a nettle leaf fraction in streptozotocin-diabetic rats, with a corresponding drop in blood sugar levels as compared to control (Farzami et al 2003). Details of the isolated fraction were not given.

Antiproliferative effects on prostate cells

Nettle extract has shown antiproliferative effects on prostate cells; however, the exact mechanism of action has not been fully elucidated (Lichius & Muth 1997, Lichius et al 1999). Results from several in vitro studies suggest that a combination of mechanisms is responsible. It seems likely that sex hormone binding globulin (SHBG), aromatase, epidermal growth factor and prostate steroid membrane receptors are involved in the antiprostatic effect, but less likely that 5-alpha reductase or androgen receptors are involved (Chrubasik et al 2007)

Prostate cancer

One study found that a methanolic extract of stinging nettle roots slows the progression of prostate cancer in both an in vivo model and an in vitro system (Konrad et al 2000). One study involving 20 males with prostatic adenoma found that treatment for 7 days with nettle produced a significant drop in zinc level, thought to be a result of altering zinc-testosterone metabolism and diminishing zinc secretion in adenomatous tissue (Romics & Bach 1991).

Antiviral

A lectin extracted from nettle had inhibitory effects against HIV-1, HIV-2, human cytomegalovirus, respiratory syncytial virus and influenza A virus in vitro (Balzarini et al 1992).

Antioxidant

Nettle has shown potent antioxidant activity in a range of in vitro tests (Gulcin et al 2004): 50, 100 and 250 microgram inhibited peroxidation of linoleic acid by 39%, 66% and 98%, respectively, as compared to 30% inhibition demonstrated by 60 microgram/mL of alpha-tocopherol.

In the same study, nettle was shown to scavenge free radicals, hydrogen peroxide and superoxide anion radicals and to chelate heavy metals. Ozen and Korkmaz (2003) reported that constituents from nettle can regulate glutathione reductase, glutathione peroxidase, superoxide dismutase and catalase in vivo.

The fixed oil of nettle has demonstrated strong antioxidant activity in mice treated with carbon tetrachloride, by decreasing lipid peroxidation and increasing antioxidant status (Kanter et al 2003). Nettle extract is significantly effective in preventing fibrosis in liver tissue from carbon tetrachloride damage in vivo (Turkdogan et al 2003). Dried nettle added to the diet of rats decreased cerebral free radicals after forced-swim tests (Toldy et al 2005).

Hepatoprotective

Treatment with stinging nettle effectively protected against aflatoxin-induced hepatotoxicity, as evidenced by decreased aspartate aminotransferase (AST), alanine aminotransferase (ALT) and gamma glutamyl transpeptidase (GGT) levels, and hepatic lipid peroxidation and elevated the antioxidants' levels in an animal model (Yener et al 2009). These findings were confirmed by histological observation. One mechanism proposed to account for this observation is nettle-maintained antioxidant enzyme activity (superoxide dismutase, catalase and glutathione reductase) which protected against hepatotoxic effects induced by aflatoxin. Comparisons between groups revealed the untreated animals experienced a significant decrease in antioxidant enzyme activity, whereas no significant changes were seen with co-administration of nettle treatment.

CLINICAL USE

Different parts of the nettle herb have been used for different indications. Some evidence comes from traditional usage; however, most recent research efforts have investigated various nettle preparations in urological and rheumatological conditions.

Arthritic conditions

Traditionally, nettle herb and leaf have been used to treat painful joint diseases, but scientific investigation has only just begun to determine whether there is a demonstrable benefit with its use.

One randomised, double-blind crossover study involving 27 patients with osteoarthritic pain at the base of the thumb or index finger compared topical applications of stinging nettle leaf with placebo, used daily for 1 week. After a 5-week washout period, treatments were then reversed. Nettle application used for 1 week showed reduction in pain and disability and produced significantly superior results to placebo (Randall et al 2000). An open study of 17 patients reporting beneficial effects with the nettle sting of *U. dioica* showed that a transient urticarial rash can be associated with topical use (Randall et al 1999). It is suspected that a counterirritant effect is chiefly responsible.

In a multicentre study of 152 subjects with degenerative rheumatic conditions, 1.54 g dried nettle herb extract produced a subjective improvement in 70% of cases after 3 weeks.

Most recently, a randomised, controlled, single-blind pilot study investigated the feasibility of conducting research to determine the effect of the sting of *Urtica dioica*, for chronic knee pain. Patients were instructed to apply a specific number of nettle (*Urtica dioica*) leaves to the affected area, or

placebo intervention with *Urtica galeopsifolia* daily for 1 week. The effect of *U. dioica* did not appear to be superior to the control treatment; however, the authors suggested several possible interpretations of this negative result. Importantly, during the study it was found that the choice of placebo was poor as *Urtica galeopsifolia* had a stinging irritant effect similar to stinging nettle. Next, there was the possibility of inadequate treatment as researchers found it difficult to supply well-grown nettles in late season, and not all patients used as many leaves as recommended. Finally, the study may have been underpowered to detect a statistical difference between groups.

Clearly, further clinical research is required to clarify the effectiveness of *Urtica dioica* in musculoskeletal conditions.

Commission E approved stinging nettle as supportive therapy for rheumatic ailments when used internally or applied externally (Blumenthal et al 2000).

Benign prostatic hyperplasia (BPH)

Clinical trials have used many different nettle extracts in liquid or oral dose forms. The Bazoton products (Kanoldt) have been most commonly investigated; however, there has also been some investigation with extracts including Urtica plus (Osterholz/Schwarzpharma), Urtica APS (Zyma/Novartis), Prostatin (Abbott), Prostaherb (Cesra), and Prosta Truw (Truw).

According to a 2007 systematic review, at least 40,000 men with BPH have been treated with various nettle root preparations in 34 clinical studies (Chrubasik et al 2007). Twenty-four studies were open and uncontrolled, two studies were open and controlled and six were randomised controlled studies. All studies evaluated methanolic nettle root extracts. Overall, available evidence indicates that methanolic nettle extracts are effective in BPH. Most studies report decreased residual urine volume, increased maximal urinary flow and improvements in symptom scores compared to placebo. Significant improvements in prostate size have also been reported in some open trials (ESCOP 1996–97). Further randomised studies are required to determine the significance and magnitude of these effects. Commission E approved the use of *Urtica* root for difficulty in urination in BPH stages 1 and 2 (Blumenthal et al 2000).

In combination

In practice, nettle root preparations are often prescribed in combination with other herbal medicines, such as saw palmetto or pygeum. Several clinical trials have investigated combination products which are more reflective of practice, overall producing positive results.

Nettle and pygeum

In one study, 134 patients with BPH were randomly assigned an *Urtica* and *Pygeum* preparation (300 mg *Urtica dioica* root extract combined with 25 mg *Pygeum africanum* bark extract) or a preparation containing half that dose under double-blind test conditions for 8 weeks. Both treatments significantly increased urine flow, and reduced residual urine and nocturia after 28 days, whereas after 56 days further significant decreases were found in residual urine (half-dose group) and in nocturia (both groups) (Krzeski et al 1993).

Nettle and saw palmetto extract

In 1995, an open, prospective, multicentre observational study involving 419 specialist urological practices investigated the efficacy and tolerability of a saw palmetto and nettle combination in 2080 patients with BPH (Schneider et al 1995). Herbal treatment was seen to improve pathological findings and obstructive and irritative symptoms. Both efficacy and tolerability were assessed by physicians as very good or good and most patients reported an improvement in general quality of life (QOL) and reduction in symptoms of BPH.

A randomised, multicentre double-blind study involving 543 patients with early stage BPH found that a combination of nettle and saw palmetto extract was as effective as finasteride at increasing maximum urinary flow and improving International Prostate Symptom Scores (IPSS) after 24 weeks' treatment, which continued to improve by week 48 (Sokeland 2000). Improvement in QOL scores was similarly observed with both treatments, regardless of prostate size. Overall, the two treatments only differed in regard to adverse reaction incidence, with the herbal combination much better tolerated (Sokeland & Albrecht 1997). A 2003 review concluded that a combination of nettle and saw palmetto is safe and effective for the treatment of lower urinary tract symptoms associated with BPH, comparable to the alpha-blocker tamsulosin (Bondarenko et al 2003).

A randomised, placebo-controlled, double-blind, multicentre trial in 2005 further demonstrated the effectiveness of saw palmetto fruit (160 mg) and nettle root (120 mg) for lower urinary tract symptoms due to prostate enlargement (Lopatkin et al 2005): 257 men aged 50 years or more were randomised to take either two capsules of the study medication (320 mg saw palmetto and 240 mg nettle root) daily or placebo for 24 weeks. Men on the treatment experienced a 35% reduction in symptoms — most notably intermittency, hesitancy, urgency and nocturia — compared to 24% for placebo. At the end of the 24-week period, an open trial was conducted for an additional 24 weeks and all men were given the herbal medicine. Those previously taking placebo reported significant improvements when switched to the study medication.

Allergic rhinitis

A double-blind randomised study showed that a freeze-dried preparation of nettles improved global assessments of allergic rhinitis after 1 week's therapy (Mittman 1990).

OTHER USES

Diarrhoea, dysentery and diseases of the colon, internal bleeding, chronic skin eruptions such as eczema, discharges and arthritic conditions.

DOSAGE RANGE

Leaf
- dry extract: 0.6–2.1 g/day in divided doses; or
- liquid extract (1:2): 15–40 mL/week.

Root
- Although Commission E recommend 4–6 g/day cut root for symptoms of BPH, doses up to 18 g/day have been used (www.phytotherapies.org June 2003).

TOXICITY
Insufficient reliable evidence is available.

ADVERSE REACTIONS
One report states that gastrointestinal discomfort, allergic reactions, urticaria, pruritus, oedema and decreased urine volume are possible (Ernst et al 2001).

Clinical studies in BPH with herbal combinations containing nettle have found that only 0.72–3.7% experience mild adverse effects.

Urticaria due to stinging nettle
A frequent cause of contact urticaria is skin exposure to the stinging nettle. The urticaria is accompanied by a stinging sensation lasting longer than 1/2 h. Part of the immediate reaction to nettle stings is due to histamine introduced by the nettle (Oliver et al 1991). It has also been found that both hair and plant extracts of nettle contain high levels of leukotriene B4 and C4, besides histamine, which add to the irritant effects (Czarnetzki et al 1990).

SIGNIFICANT INTERACTIONS
Controlled studies are not available; therefore, interactions are based on evidence of activity and are largely theoretical and speculative.

Diuretic medicines
Potentiated effects are theoretically possible — observe patients taking this combination.

Antihypertensive medicines
Additive effects are theoretically possible — observe patients taking antihypertensives concurrently.

Finasteride
Additive effects are theoretically possible, although the interaction may be beneficial.

CONTRAINDICATIONS AND PRECAUTIONS
People with known sensitivities or allergies to stinging nettle should use this herb cautiously.

PREGNANCY USE
Use of nettle during pregnancy is contraindicated because of its effects on hormones (WHO 2003).

PATIENTS' FAQs
What will this herb do for me?

Nettle leaf may reduce pain in osteoarthritis when applied topically for 1 week, whereas oral preparations of nettle root in combination with saw palmetto or pygeum reduce symptoms of BPH. Internal preparations may also reduce symptoms of allergic rhinitis, according to one human study.

When will it start to work?

Topical applications of the leaf in osteoarthritis have been shown to work after 1 week, whereas benefits in BPH require at least 28 days' treatment.

Are there any safety issues to be concerned about?

Local application of nettle can be irritating and cause contact urticaria, but preparations taken internally seem generally well tolerated.

PRACTICE POINTS/PATIENT COUNSELLING
- Preliminary research has demonstrated anti-inflammatory, analgesic and antiviral activities for nettle.
- Several test tube studies have shown that it reduces prostate cell proliferation and slows the progression of prostate cancer in both an in vivo model and an in vitro system.
- The aerial parts are most commonly used to relieve symptoms of arthritis, whereas the root is used for BPH symptom relief.
  - There is good evidence that stinging nettle extracts provide significant symptom relief in BPH and some studies indicate a possible reduction in prostate size.
- Application of nettle leaf for 1 week reduced pain and disability in arthritis under double-blind test conditions.
- One double-blind study found that nettle reduced symptoms of allergic rhinitis.
- Studies using nettle root in combination with saw palmetto or pygeum have shown positive results in BPH.

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Taurine

BACKGROUND AND RELEVANT PHARMACOKINETICS

Taurine occurs as one of the most abundant free amino acids in a wide variety of animal tissues; it is mostly absent from plants (Bouckenooghe et al 2006). In man and other mammals, the highest taurine concentrations are found in heart, retina, spleen and bone marrow (Timbrell et al 1995). Blood cells such as platelets and leucocytes are also very rich in taurine.

Traditionally taurine has been regarded as an end product of methionine metabolism. Other pathways for taurine biosynthesis exist but they have not been fully characterised and in mammals the cysteinsulfinate pathway seems to be the major pathway (Brosnan & Brosnan 2006).

There is marked variation in taurine biosynthesis in different organs and it is species- and age-dependent. The activity of cysteine sulfinic acid decarboxylase, a key enzyme in the biosynthesis of taurine from cysteine (Lambert 2004), is low in the liver and brain of human fetuses, infants and adults. The extent to which taurine can be synthesised by man is unknown at present.

Taurine does not undergo any major metabolic biotransformation, although a small amount is deaminated to isethionic acid. As taurine is metabolically inert, free taurine is readily excreted in the urine. The kidney is the major organ involved in regulating taurine levels (Chesney et al 1985, Rozen & Scriver 1982) and excess dietary taurine is excreted in the urine (Sturman 1988).

A small amount of taurine is also degraded by intestinal bacteria to sulfate, which is absorbed from the intestine and excreted in urine. The high tissue taurine levels in both mature and newborn animals

have led to much speculation about possible roles of taurine in brain, retina, heart and skeletal muscle (Grimble 2006).

CHEMICAL COMPONENTS

2-Aminoethanesulfonic acid

FOOD SOURCES

Taurine does not need to be supplied in the diet of man as it can be derived indirectly from dietary precursors. Dietary taurine is found preformed in considerable quantities in meat, fish and seafood (Roe & Weston 1965). Daily intake of preformed taurine can be 40–400 mg/day (Hayes & Trautwein 1994, Rana & Sanders 1986).

DEFICIENCY SIGNS AND SYMPTOMS

Since the 1970s there have been several reports documenting degeneration of the retina in taurine-deficient cats. Studies indicated that cats have a limited ability to synthesise taurine, and develop low plasma and tissue concentrations when fed taurine-free diets (Knopf et al 1978). The animals showed growth retardation and developed retina degeneration that eventually led to blindness. The retina degeneration could be prevented or reversed by the addition of preformed taurine to the diets, but not by feeding methionine or cysteine.

Deficiency

Taurine deficiency manifests as neuronal dysfunction. This has been demonstrated in a study of children receiving parenteral nutrition without supplemental taurine that developed low taurine plasma levels and neuronal (especially retinal) dysfunction, which could be counteracted by taurine supplementation (Geggel et al 1985).

Taurine deficiency has been reported in parenteral nutrition as taurine is not routinely added to the parenteral formulations (Lloyd & Gabe 2007).

Taurine deficiency can present in infants with cholestatic disease and this can be prevented by parenteral supplementary taurine; extensive gastrointestinal surgery can also result in taurine deficiency due to increased loss of bile acids (Lloyd & Gabe 2007, Schneider et al 2006).

MAIN ACTIONS

Many studies report that taurine is involved in a wide variety of biological processes although the exact mechanisms of action are usually not well defined.

Taurine has been proposed to have numerous roles such as a membrane stabiliser, a neurotransmitter/neuromodulator, an intracellular osmolyte and an antioxidant and may have a number of other roles including immunomodulation and growth modulator (Bouckenooghe et al 2006, Huxtable 1992, 1996). The evidence that taurine is indispensable in human nutrition remains unclear although dietary taurine has been shown to play an important part in maintaining body taurine pools.

Bile acid conjugation

Despite extensive studies on the proposed functions of taurine, the only well-defined role for taurine is conjugation with bile acids. Taurine is preferentially conjugated with bile acids in the liver, forming predominantly taurocholic acid, prior to excretion in the bile (Bouckenooghe et al 2006). Bile acids have an important role in the emulsification of dietary fat.

OTHER ACTIONS

Animal studies indicate that taurine supplementation may result in lower plasma lipid levels (Murakami et al 2002) and improve insulin sensitivity (Anuradha & Balakrishnan 1999, Nakaya et al 2000).

The compound taurine chloramine (Tau-Cl) is reported to act as an antioxidant; it is produced when hypochlorous acid produced in the 'oxidant burst' of stimulated neutrophils and monocytes, interacts with taurine (Grimble 2006). Studies report that Tau-Cl down-regulates the production of pro-inflammatory mediators and to also have antibacterial properties (Schuller-Levis & Park 2004).

Cell membrane stabilisation

Taurine reportedly acts as a modulator of membrane excitability in the central nervous system by inhibiting the release of other neurotransmitters and decreasing mitochondrial release of calcium (Grimble 2006, Muramatsu et al 1978).

Osmoregulation

It has been suggested that taurine plays an important role in osmoregulation due to its biophysical and biochemical properties (Huxtable 1992); however, this characteristic may be significant in some species and not in others.

Calcium modulation

Taurine is a modulator of intra- and extracellular calcium levels and is able to both increase Ca^{2+} availability and resist against Ca^{2+} overload, depending on the circumstances (Bradford & Allen 1996).

Xenobiotic conjugation

Taurine can conjugate with xenobiotics and animal studies indicate that this is to a varying degree, being dependent on the animal species (Nakashima et al 1982).

CLINICAL USE

Deficiency: treatment and prevention

Taurine deficiency has not been significantly investigated in man, so the information is generally derived from in vitro and animal studies. Taurine deficiency may be reflected by low plasma levels and these can be normalised by supplementary taurine.

Growth and development

Findings from animal studies have shown that maternal diet supplemented with taurine during late gestation resulted in higher fetal plasma taurine

levels and the offspring had increased postnatal growth, although the mechanism for this has not been elucidated (Hultman et al 2007).

Adult humans have a low activity of hepatic cysteine sulfinic acid decarboxylase and infants, especially premature infants, possess even lower enzyme activity. It has therefore been suggested that infants and particularly premature infants may have a greater requirement for preformed taurine than adults (Sturman et al 1975).

A systemic review by Verner et al (2009) assessed the effect of supplemental taurine versus no supplementation on the growth and development of preterm or low birth weight infants who were fed via enteral and parenteral nutrition. The authors identified nine small studies in which supplemental taurine was given with formula milk via enteral feeding in eight studies and supplemental taurine via parenteral nutrition in one study. Meta-analyses of these randomised or quasi-randomised controlled trials showed that supplemental taurine did not result in improved outcomes. However, the infants in these studies were clinically stable and the majority were greater than 30 weeks gestational age at birth and it may be that taurine requirements are different among infants who are ill or in other sub-groups.

Cardiovascular disease (CVD)

Various studies have indicated reduced CVD risk from supplementary taurine intake alone or in combination with $n-3$ polyunsaturated fatty acids (PUFA) (Militante & Lombardini 2004, Mizushima et al 1997). Studies by Yamori et al (2001, 2006) found urinary taurine excretion as the most significant single factor to correlate inversely with ischaemic heart disease (IHD) mortality and they also highlighted the benefits of combined taurine and $n-3$ fatty acids with respect to IHD mortality.

Elvevoll et al (2008) studied hypolipidaemic and anti-atherogenic effects of taurine and $n-3$ fatty acids in 75 healthy adults in a 7-week double-blind and parallel intervention trial where one group received $n-3$ PUFA, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) (1.1 g EPA + DHA/day) and the second group received both $n-3$ and taurine (425 mg/day). The results of this study demonstrated the beneficial effect of $n-3$ combined with taurine producing significant reductions in total cholesterol, low-density lipoprotein (LDL) cholesterol and apolipoprotein (apo) B in the $n-3$ + taurine group compared to the $n-3$ group alone.

Hypertension

In a randomised, controlled study of 31 borderline hypertensive adults and normal adults, 6 g taurine was given daily for 7 days; although the normal subjects did not experience any effects, the intervention group experienced a significant decrease in blood pressure and serum catecholamines (Fujita et al 1987).

In another randomised, controlled study of 11 healthy adult males taking 6 g taurine/day in presence of a high fat, high cholesterol diet for 3 weeks, there was no change in blood pressure but there was a significant increase in very low-density lipoproteins (VLDLs) and triglycerides (Mizushima et al 1996).

Obesity

In a small randomised, controlled study, 15 healthy overweight adults were treated with 3 g taurine/day for 7 weeks resulting in significant decrease in serum triglycerides although there was no change in high-density lipoprotein (HDL) cholesterol or fasting glucose (Zhang et al 2004a). In a somewhat larger study of 30 overweight or obese non-diabetic young subjects, taurine supplementation (3 g/day; 1 g × 3 times/day) over a 7-week period resulted in a beneficial effect on lipid metabolism and a decrease in body weight (Zhang et al 2004b).

Diabetes

In contrast to findings from animal studies, human studies do not altogether support a role for taurine in the management of diabetes; a study of 22 patients with type 2 diabetes who were treated with 3 g taurine/day for 4 months found no effect on glycated haemoglobin A1c (HbA_{1c}) or fasting glucose (Chauncey et al 2003). Likewise, a double-blinded, randomised, crossover study of 20 non-diabetic subjects who were overweight first-degree relatives of type 2 diabetes mellitus (T2DM) patients received a daily supplementation of 1.5 g taurine or placebo; the results of this study showed that taurine supplement did not exert any effect on blood lipid levels or insulin secretion or sensitivity in subjects with both genetic and some non-genetic factors predisposing them to T2DM (Brøns et al 2004). Similarly, Spohr et al (2005) showed that taurine supplementation had no effect on platelet aggregation in 20 healthy men with a predisposition to T2DM. A study by Franconi et al (1995) looking at 1.5 g/day of taurine supplementation for 90 days in 39 patients with insulin-dependent diabetes mellitus (IDDM), with healthy, age and sex-matched subjects, found that taurine reduced platelet aggregation in patients with diabetes whereas aggregation was not affected in the controls.

Epilepsy

Several studies have investigated the role of taurine supplementation in the management of seizure disorders, overall producing inconsistent results. In some studies, patients with severe intractable epilepsy were administered taurine either orally or intravenously, varying in both duration and dose (from 200 mg/day and up to 21 g/day), making comparisons difficult. Additionally, most studies were uncontrolled and flawed with regard to methodology thereby hindering accurate interpretation (Fariello et al 1985). Some studies reported a reduction in seizure frequency (Takahashi & Nakane 1978), whereas others did not observe any benefit (Mantovani & DeVivo 1979).

The optimal dose of taurine supplementation in the management of epilepsy may be in the range of 100–500 mg/day with a recent study by Gaby (2007) noting loss of anti-seizure activity in some patients when the dose was increased to above 1.5 g/day. According to this study, beneficial effects

are relatively short lasting and are not maintained beyond a few weeks of treatment. Additional studies are required to clarify the role of taurine supplementation in practice.

DOSAGE RANGE

Taurine is administered orally usually in divided doses; adult dosage is generally 500 mg to 3 g daily and paediatric dosage 250 mg to 1 g daily and these are dependent on the size and age of the child.

There appear to be very few health concerns regarding taurine supplementation, although safety has been of interest recently because of the high intakes that can be easily consumed from some sports drinks (Munro & Renwick 2006).

TOXICITY

In a risk assessment by Shao & Hathcock (2008) the following recommendations have been made: no observed adverse effect level (NOAEL) and lowest observed adverse effect level (LOAEL) > 10 g taurine/day; observed safe level (OSL) 3 g/day; upper level for supplements (ULS): 3 g/day.

ADVERSE REACTIONS

Taurine administration appears to be safe, even at higher doses. Children should be monitored for any adverse side effects and supplementation ceased if any adverse effects develop.

At dosages of 2 g/day, patients with psoriasis experienced intense, temporary itching (Kendler 1989); dosages of 1.5 g taurine/day caused nausea, headache, dizziness and gait disturbances in some epileptic patients (Van Gelder et al 1975).

SIGNIFICANT INTERACTIONS

Controlled studies are not available and at present there are no known drug interactions with taurine.

CONTRAINDICATIONS AND PRECAUTIONS

High doses of taurine (10 g/day for 6 months) have been taken without any major side effects (Durelli et al 1983); the longest duration recorded has been 1 year (Colombo et al 1988). Many commercially available energy drinks contain substantial amounts of supplementary taurine (1000 mg/L) and as there is very little information about the effects of these doses, the young, people who are immunocompromised, pregnant and nursing mothers should consult a relevant health professional before excessive intake. People with psoriasis and epilepsy should avoid high intakes of taurine.

PREGNANCY USE

At present there is no evidence to prove the benefit of taking supplementary taurine during pregnancy.

PATIENTS' FAQs

What will this supplement do for me?

Decreased plasma levels can be normalised by taurine supplementation. There is some evidence that taurine may be a useful treatment in CVD.

When will it start to work?

Plasma taurine levels can increase within a week of taking supplementary taurine.

PRACTICE POINTS/PATIENT COUNSELLING

- Taurine can be readily obtained by eating meat, fish and seafood.
- Most people are able to produce taurine naturally; however, young infants are limited in their ability to produce taurine and obtain their dietary taurine from either breast milk or supplemented milk formulas
- Plasma taurine levels can be low in some illnesses and conditions (such as sepsis) and can be restored with supplementary taurine.
- At present there is no evidence to prove the benefit of taking taurine during breastfeeding.
- Traditionally taurine has been used in CVD, hypertension and hyperlipidaemia.
- 'Energy' soft drinks may contain taurine as well as caffeine although the potential interactions between these two ingredients have not been determined.

Are there any safety issues?

Generally taurine supplementation has a good safety profile.

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Tea tree oil

HISTORICAL NOTE The Bundjalong Australian Aboriginal people of northern New South Wales knew of the medicinal qualities of this plant's leaves for many centuries and used it to treat burns, cuts and insect bites. It was not until the 1700s that it became known in the Western world as 'tea tree' because Captain Cook found its aromatic leaves an enjoyable substitute for real tea. The first official report of its medicinal use appeared in the *Medical Journal of Australia*, in 1930, when a Sydney surgeon wrote of its impressive wound healing and antiseptic qualities (Murray 1995). In modern times, tea tree oil has become widely accepted as a standard treatment for wounds and minor skin infections.

COMMON NAME
Tea tree

OTHER NAMES
Australian tea tree oil, melaleuca, melasol, narrow-leaved paperbark, paperbark tree oil, punk tree, ti tree oil

BOTANICAL NAME/FAMILY
Melaleuca alternifolia (family Myrtaceae)

PLANT PARTS USED
Essential oil from leaves and branches

CHEMICAL COMPONENTS
Tea tree oil contains many active constituents, including cineole, alpha-cadinine, terpinenes, pinenes, alpha-terpineol, aromadendrene, terpinenols and terpinolene (Duke 2003). Purified components have been found to have greater antibacterial and fungicidal activities than the whole oil,

with terpinen-4-ol being the most active (Loughlin et al 2008, Terzi et al 2007).

Antifungal and antibacterial

The in vitro evidence of antifungal and antibacterial activities is overwhelming. In vitro results find that tea tree oil has activity against a range of yeasts and fungi found in common mucosal and skin infections, such as *Corynebacterium* spp., *Klebsiella pneumoniae*, *Micrococcus* spp. (*M. luteus*, *M. varians*), *Propionibacterium acnes*, *Streptococcus pyogenes*, *Trichomonas vaginalis*, *Pseudomonas aeruginosa*, *A. baumannii*, *Staphylococcus* spp. (*S. aureus*, *S. capitis*, *S. epidermidis*, *S. haemolyticus*, *S. hominis*, *S. marcescens*, *S. saprophyticus*, *S. warneri* and *S. xylosus*) and *Candida* spp. (Bagg et al 2006, Carson et al 2006, Concha et al 1998, De Mondello et al 2003, Hada et al 2001, Hammer et al 1996, 1998, Messager et al 2005, Murray 1995, Papadopoulos et al 2006, Tortorano et al 2008). Importantly, tea tree oil has been shown to have activity against methicillin-resistant *Staphylococcus aureus* (MRSA) and coagulase-negative *Staphylococci* (CoNS) (Brady et al 2006, Loughlin et al 2008).

It is suggested that the antibacterial activity of tea tree is due to its ability to effectively bind to the bacterial cell wall (Chung et al 2007). Tea tree oil disrupts the permeability barrier of cell membrane structures of microorganisms and denatures the proteins (Carson et al 2002, Cox et al 2000, Gustafson et al 1998, Tao et al 2006). This activity is similar to disinfectants such as chlorhexidine and quaternary ammonium compounds.

Antiviral

An in vitro study has identified activity against herpes simplex virus (HSV) types 1 and 2 (Schnitzler et al 2001).

Oestrogenic and antiandrogenic activities

Studies in human cell lines have indicated that tea tree oil has oestrogenic and antiandrogenic activities and it is suggested that this may have contributed to treat the cases of prepubertal gynaecomastia, with topical use (Henley et al 2007).

Other actions

Tea tree oil is reported to have anti-inflammatory activity (Carson et al 2006) and animal studies have demonstrated that inhalation of tea tree oil has both anti-inflammatory and immunomodulatory actions that are likely to be mediated by the hypothalamic pituitary axis (Golab & Skwarlo-Sonta 2007).

CLINICAL USE

Topical tea tree oil preparations have been investigated in a number of clinical studies, either as the oil itself or as an ingredient of gels, creams or ointments. In vitro studies suggest that the penetration of topical tea tree oil components through the skin is limited (Cross et al 2008).

Acne vulgaris

A randomised, double-blind, placebo-controlled study of 60 patients found that a topical 5% tea tree oil gel was an effective treatment of mild-to-moderate acne vulgaris (Enshaieh et al 2007). This result is supported by a single-blind, randomised clinical trial involving 124 patients with mild-to-moderate acne and showed that a similar gel significantly improved the condition and reduced the number of acne lesions. These effects were similar to 5% benzoyl peroxide lotion, but tea tree oil gel was better tolerated and produced fewer side effects (Bassett et al 1990).

Tinea pedis

Under double-blind, randomised test conditions, 104 subjects with tinea pedis (athlete's foot) used 10% w/w tea tree oil cream or 1% tolnaftate or placebo creams as treatment (Tong et al 1992). In this study, significantly more tolnaftate-treated patients (85%) than tea tree oil- (30%) and placebo-treated (21%) patients showed conversion to negative culture at the end of therapy. However, tea tree oil cream reduced symptoms as effectively as tolnaftate 1%. A more recent randomised, double-blinded, controlled study by the same group used a higher concentration of tea tree oil (25% and 50%) for the treatment of interdigital tinea pedis in 158 patients over 4 weeks (Satchell et al 2002a). In the 50% tea tree oil group, 68% of patients had a significant response and 64% achieved negative mycology. In the 25% tea tree group, 72% of patients responded and 50% were cured. The placebo responder rates were 39% and 31%, respectively, with 3% of patients using tea tree developing dermatitis. It is suggested that the fungicidal activity of tea tree and other essential oils can be enhanced using footbaths heated to 42°C (Inouye et al 2007).

Toenail infection (onychomycosis)

A randomised, double-blind multicentre study involving 177 volunteers found that 6 months' treatment with 1% clotrimazole solution (applied twice daily) or 100% tea tree oil (applied twice daily) produced similar results, improving nail appearance and associated symptoms (Buck et al 1994). Additionally, 3 months after either treatment ceased, continued improvement or complete resolution was observed in approximately half of participants. One randomised, double-blind, placebo-controlled study investigated the effects of a combined tea tree oil (5%) and butenafine hydrochloride (2%) cream in chronic toenail onychomycosis and found that after 6 weeks, 80% of patients achieved a cure compared with none using placebo cream (Syed et al 1999).

MRSA infection

Washing with 5% tea tree oil (TTO) has been shown to be effective in removing MRSA on the skin (Thompson et al 2008) and tea tree oil has been effectively used against biofilm formation on tympanostomy tubes in vitro (Park et al 2007). A combination of 4% tea tree oil nasal ointment and 5% tea tree oil body wash was found to be superior to the standard 2% mupirocin nasal ointment and triclosan body wash used for the eradication of MRSA (Caelli et al 2000).

A recent review concluded that tea tree oil was not statistically superior to the standard treatment mupirocin for MRSA (Flaxman & Griffiths 2005). The paper reported on two RCTs (n = 30, n = 224), both of which demonstrated that tea tree oil was as effective as mupirocin. In the larger trial, 224 patients were given either mupirocin 2% nasal ointment, chlorhexidine gluconate 4% soap and silver sulfadiazine 1% cream or tea tree 10% cream and tea tree 5% body wash for 5 days (Dryden et al 2004). Rates of MRSA clearance were similar: 41% in the tea tree group and 49% using standard treatment. Mupirocin was significantly more effective at clearing nasal carriage (78%) than tea tree cream (47%); however, tea tree treatment was more effective than both chlorhexidine and silver sulfadiazine at clearing superficial skin sites and skin lesions. Although encouraging, more large clinical trials are needed to examine the efficacy of tea tree in both treating and preventing MRSA infection (Thompson et al 2008).

Although tea tree oil may be an effective antimicrobial agent when appropriately used at bactericidal concentrations, its application at sublethal concentrations may contribute to the development of antibiotic resistance in human pathogens (McMahon et al 2007).

Vaginitis and cervicitis

Clinical data support the use of tea tree oil for vaginitis and cervicitis caused by *Trichomonas vaginalis* or *Candida albicans* (WHO 2003, Vila & Canigueral 2006). An open study found that intravaginal application of tampons saturated in a diluted emulsified solution successfully healed vaginitis and cervicitis (n = 130) caused by *T. vaginalis*. Vaginal pessaries containing 0.2 g essential oil inserted nightly eradicated symptoms of leucorrhoea and burning in 86% of women with *C. albicans* vaginitis after 30 days with 75% of women also becoming free of infection (WHO 2003).

A case report shows that a 5-day course of 200 mg tea tree oil in a vegetable oil base inserted into the vagina may also be successful at treating vaginal candidiasis with eradication of anaerobic bacterial vaginosis being confirmed after 1 month (Blackwell 1991).

Cystitis

A randomised, double-blind study investigated the effects of tea tree oil, administered as 8 mg essential oil (taken three times daily) in an enteric-coated capsule, in 26 women with chronic idiopathic colibacillary cystitis (Belaiche 1988). After the 6-month test period, 54% of women receiving active treatment were symptom free compared with only 15% receiving placebo. Although symptom free, 50% of women in the tea tree group still showed evidence of infection.

Gingivitis

Tea tree oil was as effective as chlorhexidine against *Streptococcus mutans*, the bacteria that causes gingivitis, in a controlled study of 30 individuals (Groppo et al 2002). A more recent double-blind, randomised, longitudinal study evaluated and compared the effects of tea tree oil gel (2.5%) and chlorhexidine gel (0.2%) in 49 patients with severe chronic gingivitis (Soukoulis & Hirsch 2004). Subjects brushed with the tea tree, chlorhexidine or placebo gel, twice daily, for a period of 8 weeks. Tea tree oil significantly reduced the papillary bleeding index and gingival index, but did not reduce plaque.

Dandruff

Tea tree oil is effective for the treatment of dandruff. A randomised, single-blind, parallel-group study investigated the efficacy of tea tree oil shampoo (5%) and placebo in 126 patients with mild-to-moderate dandruff over 4 weeks (Satchell et al 2002b). The tea tree oil group achieved a 41% improvement as compared to 11% in the placebo group, with no adverse effects.

OTHER USES

Cold sores

Since tea tree oil exhibits antiviral activity in vitro, tea tree oil preparations have been used in the treatment of herpes simplex. Clinical trials investigating tea tree oil for this indication are not available, so it is unknown whether effects are clinically significant.

Head lice eradication

In test tube studies, topical application of tea tree oil was extremely effective against head lice, with 93% of lice and 83% of eggs destroyed (Veal 1996). Phenols, phenolic ethers, ketones and oxides appear to be the major toxic components responsible for this activity. Using a mite chamber assay, tea tree oil was also found to be effective against both head lice and dust mites (Williamson et al 2007). While there is anecdotal evidence for its clinical use, this has not yet been confirmed by clinical trials (Centre 2008).

Hair follicle mite eradication (ocular demodecosis)

In a retrospective review of 11 cases, lid scrub with 50% tea tree oil combined with daily lid hygiene and tea tree shampoo for 4 weeks was observed to effectively eradicate the hair follicle mite *Demodex folliculorum* and result in subjective and objective improvements (Gao et al 2007).

Dermatitis

Tea tree oil may be an effective treatment for dermatitis in dogs. Tea tree oil cream (10%) was applied, twice daily, for 4 weeks to 53 dogs suffering from chronic dermatitis, allergic dermatitis, interdigital pyoderma, acral lick dermatitis and skinfold pyoderma (Fitzi et al 2002). At the end of the trial, 82% of the animals had a good or very good response to treatment with most symptoms disappearing, although two dogs experienced local irritation. Another trial by the same research team again evaluated the tea tree cream and blinded the study with a commercial skin care cream (Reichling et al 2004). Fifty-seven dogs were involved in this study and again the results were similar, with drastically reduced dermatitis in 71% of animals as compared to 41% using the control cream. A local reaction was reported in one dog.

Wart eradication

There is a report that daily topical application of tea tree oil for 12 days successfully eradicated warts on the hand of a paediatric patient (Millar & Moore 2008).

DOSAGE RANGE

Tea tree oil is used in a variety of forms, such as gels, creams, ointments, oral rinses, soaps, shampoos and paints. Minimum bactericidal concentrations are generally 0.25%.

- Onychomycosis: 100% essential oil applied twice daily.
- Tinea pedis: 10% essential oil in cream base applied twice daily.
- Acne: 5% essential oil in cream or gel base applied daily.
- Vaginitis (*Candida albicans* or *Trichomonas vaginalis*): intravaginally applied tampons saturated in a 1% emulsified solution, vaginal pessaries containing 0.2 g essential oil.
- Cervicitis (*Candida albicans* or *Trichomonas vaginalis*): intravaginally applied tampons saturated in a 20% emulsified solution.

TOXICITY

Tea tree oil should not be ingested. Accidental ingestion has resulted in confusion, disorientation, general malaise and coma, according to case reports (WHO 2003).

One case has been reported of an infant ingesting less than 10 mL of 100% oil, which resulted in confusion and an inability to walk within 30 min, followed by a full recovery within 5 h (Jacobs & Hornfeldt 1994).

ADVERSE REACTIONS

Anecdotal evidence from almost 80 years of use suggests that the topical use of the oil is relatively safe, and that adverse events are minor, self-limiting and occasional (Hammer et al 2006). Contact dermatitis is possible in sensitive individuals (Hammer et al 2006, Williams et al 2007) and it suggested that this is underreported and that tea tree oil should be included in patch testing. Oxidised monoterpenes are likely to be the sensitising agents (Reichling et al 2006) as tea tree oil from freshly opened products elicits no or weak reactions. It is therefore suggested that patch testing needs to be done with oxidised tea tree oil (Rutherford et al 2007).

Three cases of prepubertal gynaecomastia have been reported in boys who had used topical products containing lavender and tea tree oils with the gynaecomastia resolving after the products were discontinued (Henley et al 2007).

SIGNIFICANT INTERACTIONS

None known.

CONTRAINDICATIONS AND PRECAUTIONS

Caution should be exercised if applying the oil to eczematous or inflamed skin as it may cause irritation. It is suggested that a small amount be first applied to a test patch, to determine whether irritation will occur, as contact dermatitis has been reported.

PRACTICE POINTS/PATIENT COUNSELLING

- 100% tea tree oil is a safe and effective alternative to clotrimazole for the treatment of toenail onychomycosis.
- Extensive in vitro testing has found significant activity against a wide range of bacterial and fungal microorganisms, such as common skin pathogens.
- 5% tea tree oil gel has been shown to significantly improve acne vulgaris, with effects similar to 5% benzoyl peroxide lotion.
- Clinical evidence supports the use of tea tree oil preparations in *Candida albicans* or *Trichomonas vaginalis* vaginitis and cervicitis, cystitis and MRSA infection. It may also be useful in herpes simplex and head lice, but clinical data are unavailable.
- Tea tree oil should not be ingested other than in capsule form under professional supervision and a test patch is advised before widespread topical application.

PREGNANCY USE

Insufficient reliable information is available to determine safety.

PATIENTS' FAQs

What will tea tree oil do for me?

Tea tree oil is an antiseptic substance that is effective against a wide range of common bacterial and fungal organisms. Scientific evidence shows that it is an effective treatment for acne, fungal infections of the toenails, *Candida albicans* or *Trichomonas vaginalis* vaginitis and cervicitis, cystitis and MRSA infection. It is also used to treat cold sores and head lice.

When will it start to work?

This will depend on the indication it is being used to treat. In some cases, clinical tests are not available, so it is uncertain when, if any, effects are seen.

Are there any safety issues?

Tea tree oil should not be ingested orally and used with caution on inflamed and sensitive skin.

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Thyme

HISTORICAL NOTE Although thyme has been used as a cooking spice for centuries in Europe, it is also used medicinally to treat common infections, coughs, bronchitis and asthma. The 17th century herbalist Nicholas Culpeper recommended thyme for whooping cough, gout, stomach pains and shortness of breath. It was also used in perfumes and embalming oils. In medieval times the plant was seen as imparting courage and vigour (Blumenthal et al 2000).

COMMON NAME
Thyme

OTHER NAMES
Common thyme, garden thyme, farigola, folia thymi, gartenthymian, herba thymi, almindelig timian, thym, thymian, thymianblätter, timo

BOTANICAL NAME/FAMILY
Thymus vulgaris (family Lamiaceae)

PLANT PARTS USED
Leaves and flowering tops

CHEMICAL COMPONENTS
The primary constituents are the volatile oils (1–2.5%), which include phenols (0.5%), namely thymol (30–70%), eugenol and carvacrol (3–15%), also flavonoids, apigenin, luteolin and saponins and tannins. Rosmarinic acid, caffeic acid and calcium are also found in significant quantities (Duke 2003). The herb also contains bitter principles and salicylates.

MAIN ACTIONS
Although thyme has not been significantly investigated in human studies, there has been some investigation into the activity of thymol and the volatile oil component of the herb. It is not known whether results obtained for these constituents are representative for the crude herb, but they provide some further understanding. Both the essential oil and thymol are ingredients in many proprietary products.

Antitussive and antispasmodic effects
These actions have been attributed to the phenolic compounds in thyme (WHO 2003). Antispasmodic effects on trachea and guinea pig ileum have been demonstrated for these constituents and for the whole extract of thyme (Engelbertz et al 2008).

Expectorant
The saponin content is believed to have expectorant activity, as demonstrated in animal studies. An in vivo trial has demonstrated improved expectoration and mucociliary clearance (Wienkotter et al 2007).

Antibacterial
In vitro tests have demonstrated activity of thyme extract against *Escherichia coli*, *Listeria monocytogenes*, *Streptococcus mutans* and *Salmonella enterica* (Burt et al 2005, 2007, Fabian et al 2006, Friedman et al 2002, Hammad et al 2007, Schelz et al 2006, Solomakos et al 2008). A review of the antibacterial and antifungal properties of the essential oil of thyme in vitro has demonstrated effectiveness against a wide range of pathogens including *Clostridium botulinum*, *E. coli*, *Haemophilus influenzae*, *Klebsiella pneumoniae*, *Salmonella typhi*, *Staphylococcus aureus* and *Candida albicans* (Kalemba & Kunicka 2003). Effects are most likely due to the eugenol, thymol and carvacrol constituents. Aqueous thyme extract also exhibited a significant inhibitory effect on *Helicobacter pylori*, reducing both its growth and its potent urease activity in vitro (Tabak et al 1996). More recently an extract of thyme was found to potentiate the anti-bacterial effects of tetracycline against methicillin-resistant *Staphylococcus aureus* in vitro (Fujita et al 2005). The compound baicalein was thought to be responsible.

Antifungal
Thymol and eugenol have demonstrated antifungal activity by establishing the ability to alter the cell wall and membrane of the yeasts *Saccharomyces cervisiae* and *Candida albicans* (Bennis et al 2004, Braga et al 2007b, Braga et al 2007a).

Antiviral
Thyme oil demonstrates antiviral activity against HSV-1, HSV-2 and an acyclovir-resistant strain of the virus (Koch et al 2007, Nolkemper et al 2006, Schnitzler et al 2007). One study found that the oil decreased plaque formation by more than 90% when preincubated with HSV-2, however no effect was observed when the oil was added prior to infection or after the absorption stage (Koch et al 2007). It was suggested that thyme essential oil interferes with the viral envelope.

Antioxidant
Three in vitro studies have investigated the antioxidant effects of thyme (Braga et al 2006a, Chizzola et al 2008, Lee et al 2005). One study found that eugenol, carvacrol, thymol and 4-allylphenol (5 μg/mL) all inhibited the oxidation of hexanal for a period of 30 days, demonstrating potent antioxidant activity comparable to alpha-tocopherol (Lee et al 2005). An in vivo study also found that thyme exerted significant antioxidant effects in a N-nitrosodiethylamine-induced oxidative stress model in rats (Rana & Soni 2008).

Astringent
The tannin content of the herb is chiefly responsible for its astringent activity.

Anthelmintic
Thymol possesses anthelmintic activity, demonstrated in vitro (Newell et al 1996).

Anti-inflammatory
Thymol has demonstrated anti-inflammatory effects in vitro by reducing elastase (Braga et al 2006b). A combination of oregano and thyme essential oils has been shown to reduce inflammation in trinitrobenzene sulfonic acid (TNBS)-induced colitis in vivo (Bukovska et al 2007). A dose of 0.2% thyme and 0.1% oregano led to a reduction in IL-1 beta, IL-6, GM-CSF and TNFalpha. The oils also decreased mortality rate, increased body weight and reduced histological damage.

OTHER ACTIONS
Thyme may possess antithrombotic properties (Naemura et al 2008).

CLINICAL USE
Thyme has not been significantly investigated in controlled studies, therefore information is generally derived from evidence of activity and traditional use, and the clinical significance is unknown.

Respiratory tract infections
Thyme extract has been used to treat the common cold, bronchitis, laryngitis and tonsillitis. It is orally ingested or used in a gargle for local activity, based on the herb's suspected antimicrobial and antitussive activities.

Bronchitis
Encouraging data have been reported for chronic bronchitis treated by thyme in combination with other herbs in large ($n > 3000$) comparative clinical trials, although no data are available for thyme as a stand-alone treatment (Ernst et al 1997). A combination of thyme and primrose root (1 mL five times/day) has been found to be beneficial in both double-blind and single-blind trials (Gruenwald et al 2005, 2006). The double-blind, placebo controlled, randomised, multicentre trial in 150 outpatients with acute bronchitis found that 58.7% of participants in the treatment group were symptom free at the end of the 7 to 9 days compared to 5.3% in the placebo group (Gruenwald et al 2005). A double-blind, placebo controlled, multicentre study investigated the efficacy of the same combination in 361 outpatients with acute bronchitis or severe cough (Kemmerich 2007). The combination successfully reduced coughing fits by 67.1% compared to 51.3% on days 7 to 9 ($P < 0.0001$). The active group reported a 50% reduction in coughing on average 2 days earlier than the placebo group. The singular effect of thyme in this formula however is uncertain.

A postmarketing surveillance study investigated the effects of a different mixture containing thyme and ivy as a syrup (Bronchipret Saft) in 1234 children and adolescents with acute bronchitis (Marzian 2007). Coughing fits reduced by 81.3% by day 10 and the responder rates for the various age groups were 92.0 to 96.5%. The singular effect of thyme in this formula however is uncertain.

Thyme is approved by Commission E in the treatment of bronchitis, whooping cough and upper respiratory tract catarrh (Blumenthal et al 2000).

Diarrhoea
The astringent activity of thyme provides a theoretical basis for its application in this condition.

Gastritis and dyspepsia
The bitter principles present in the herb and its antispasmodic activity provide a theoretical basis for its use in these conditions.

Skin disinfection (topical use)
Thyme extract has been used topically for infection control in minor wounds. The herb's antimicrobial and astringent activity provides a theoretical basis for this use.

OTHER USES
Traditionally, it has been used to aid in labour and delivery, promote menstruation and topically for warts and inflamed swellings (Fisher & Painter 1996). It has also been used to treat enuresis in children.

DOSAGE RANGE

Internal use
- Fluid extract (1:1): 1–2 mL up to three times a day.
- Fluid extract (1:2): 15–40 mL/week.
- Tincture (1:5): 2–6 mL three times daily.
- Infusion of dried herb: 1–4 g three times daily.

External use
- 5% infusion used as a compress.

ADVERSE REACTIONS
The volatile oil is considered an irritant topically and can cause nausea and vomiting, headache, dizziness, convulsions, cardiac or respiratory arrest if taken internally (Newell et al 1996). As such, the crude herb is considered far safer.

Contact dermatitis reactions have been reported with topical use (Lorenzi et al 1995).

SIGNIFICANT INTERACTIONS
Thyme may induce enzymes in phase one and two detoxification in the liver (Sasaki et al 2005). The clinical significance of this is unknown.

CONTRAINDICATIONS AND PRECAUTIONS
Contraindicated in people who are allergic to the Lamiaceae (Labiatae) family of plants. Other cautions are gastritis, enterocolitis and congestive heart failure (Ernst et al 2001).

PREGNANCY USE
Essential oil not recommended in pregnancy.

PATIENTS' FAQs
What will this herb do for me?
When taken internally, thyme is used to treat bronchitis, symptoms of the common cold, diarrhoea and dyspepsia. It is also used as an antiseptic gargle

for sore throats and can be diluted and applied externally to minor wounds.

When will it start to work?

The lack of human studies for this herb make it difficult to determine when effects will start to occur.

Are there any safety issues?

Thyme should not be used by people allergic to the Lamiaceae (Labiatae) family of plants or in pregnancy, and it should be used with caution in gastritis, enterocolitis and congestive heart failure.

PRACTICE POINTS/PATIENT COUNSELLING

- Although thyme is used as a cooking spice, it is also used medicinally to treat common upper respiratory tract infections, coughs, bronchitis and asthma, dyspepsia and diarrhoea.
- Thyme extract is used as a gargle for pharyngitis or applied topically (5% dilution) as a compress to wounds due to its antimicrobial and astringent activities.
- Thyme has not been significantly investigated in controlled trials, so much information is based on traditional use or evidence of activity.
- Thyme has antispasmodic, antimicrobial, antitussive, astringent and anthelmintic activities as demonstrated in vitro or in animal studies.

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Tribulus

HISTORICAL NOTE Widely distributed in the Mediterranean region, Middle East and southern Africa, tribulus is an important plant used in traditional Ayurvedic, Arabic and Chinese medicine. Different parts of the tribulus plant are used to treat a variety of conditions, such as cough, colicky spasms, diarrhoea, haemorrhage, cardiovascular disease, rheumatic pain, gout, various kidney disorders, including kidney stones, and as an insect repellent.

COMMON NAME
Tribulus

OTHER NAMES
Al-gutub, cats-head, devil's-thorn, devil's-weed, goathead, puncture vine, qutiba

BOTANICAL NAME/FAMILY
Tribulus terrestris (family Zygophyllaceae)

PLANT PARTS USED
Leaf or fruit

CHEMICAL COMPONENTS
Different parts of the plant contain different constituents in varying ratios. Overall, the steroidal saponin content is considered the most important and includes constituents such as protodioscin, diosgenin, yamogenin, epismilagenin, tigogenin, neotigogenin, gitogenin and neogitogenin (Miles et al 1994). More steroidal saponins have been isolated from extracts of tribulus fruit in the past 5 years (Huang et al 2003, Su et al 2008, 2009, Xu et al 2008). The significance of this has not yet been determined. Beta-sitosterol, vitamin C, potassium and calcium are also found in the herb (Li et al 1998). Two major alkaloids have been identified: harmane and norharmane (Bourke et al 1992).

Of the steroidal saponins, protodioscin is considered the chief constituent responsible for the plant's effects on libido and sexual functioning. Preliminary observations suggest that *Tribulus terrestris* grown in different soils does not consistently produce this constituent and considerable variations have been identified in commercial products (Ganzera et al 2001). Steroidal saponins consist of a furostanol- or spirostanol-based aglycone and an oligosaccharide attached to a steroid nucleus. Steroidal saponins are very common in the plant kingdom and are natural components in many foods, such as asparagus, garlic and oats.

MAIN ACTIONS
Tribulus has not undergone significant clinical investigation; therefore, evidence of activity primarily derives from animal and in vitro studies. Additionally, some studies have investigated the pharmacological effects of the isolated saponin content.

Increases libido and enhances sexual function
Administration of tribulus extracts to animals improves libido and spermatogenesis. The exact mechanism by which tribulus influences sexual behaviour is not known, but increasing androgenic status and nitric oxide (NO) release appear to be chiefly responsible (Gauthaman et al 2002). More specifically, some reports have suggested that increases in dehydroepiandrosterone (DHEA) and testosterone are possible (Adimoelja 2000, Gauthaman et al 2002).

The constituent protodioscin is considered the most important in this regard and is converted to DHEA. Additionally, ex vivo tests have observed pro-erectile effects with protodioscin due to increased release of NO from the endothelium and nitronergic nerve endings (Adaikan et al 2000). Hormonal effects of tribulus were tested in primates, rabbits and rats. Administration of tribulus demonstrated a statistically significant increase in testosterone and DHEA levels in the primates, an increase of these hormones in rabbits, but very little increase in rats (Gauthaman & Ganesan 2008).

In combination
A mixture of nine oriental herbs, including tribulus, was evaluated using both in vitro and in vivo experiments on laboratory animals and demonstrated an improvement in sexual activity and erectile function (Park et al 2006). It is possible that tribulus may be useful in mild-to-moderate cases of erectile dysfunction; however, further clinical testing is required.

Oestrogenic
Saponins from tribulus appear to increase follicle stimulating hormone (FSH) in women, which in turn increase levels of oestradiol (Mills & Bone 2000). The primary site of action of steroidal saponins is probably the hypothalamus (Trickey 1998).

Antimicrobial
Antimicrobial activity of organic and aqueous extracts from fruits, leaves and roots of *Tribulus terrestris* were tested. The most active extract against both gram-negative and gram-positive bacteria was ethanol extract from the fruits against *Bacillus subtilis*, *Bacillus cereus*, *Corynebacterium diphtheriae* and *Proteus*

vulgaris. The strongest antifungal activity was against *Candida albicans* (Al-Bayati & Al-Mola 2008).

Diuretic

A large oral dose of 5 g/kg tribulus was shown to have greater diuretic activity than frusemide 120 mg/kg in vivo (Al Ali et al 2003).

Urolithic

Wth regard to kidney stones, tribulus has been found to decrease the amount of urinary oxalate in rats (Sangeeta et al 1994) and produce significant dose-dependent protection against experimentally induced uroliths in animal studies (Anand et al 1994, Sangeeta et al 1994). Experimental studies further found that tribulus was effective in preventing the deposition of crystals on glass beads in the urinary bladder of rats, dissolving phosphate-type calculi in an in vitro model, and dissolving uric acid and cystine stones to some extent (Prasad & Bharathi 2007). In vitro studies using human urine suggests that the diuretic properties of tribulus may be the most crucial mechanism for preventing urinary stone formation (Joshi et al 2005).

Antispasmodic

A dose-dependent antispasmodic activity causing a significant decrease in peristaltic movements has been demonstrated with the isolated saponin content of tribulus (Arcasoy et al 1998).

Cardioprotective activity

Tribulus is shown to have some cardioprotective actions (Ojha et al 2008). A Chinese report of successful treatment of angina pectoris with the saponin content of tribulus suggests that the preparation dilates coronary arteries and improves coronary circulation (Wang et al 1990). A triterpene saponin of tribulus may play a role in cardiocyte survival during chemical hypoxia–ischaemia as demonstrated in vitro (Sun et al 2008).

In another study 10 mg/kg/day of the aqueous extract of the fruit has shown antihypertensive effects in an animal trial when compared to control. The authors concluded that effects are possibly due to inhibition of angiotensin-converting enzyme (ACE) activity (Sharifi et al 2003). More recent research demonstrates that the antihypertensive effect appears to result from a direct arterial smooth muscle relaxation possibly involving nitric oxide release and membrane hyperpolarisation (Phillips et al 2006). Tribulus saponins not only lowered serum lipidaemia, but also relieved left ventricular remodelling, and improved cardiac function in the early stage after myocardial infarct in a hyperlipaemia mouse model (Guo et al 2007). The mechanism of action is suggested to be a reduction in cardiac muscle cell apoptosis by regulating protein expressions (Guo et al 2006).

OTHER ACTIONS

Experiments with healthy mice have found that *Tribulus terrestris* significantly inhibits gluconeogenesis, influences glycometabolism and reduces triglyceride and total cholesterol levels (Li et al 2001). Tribulus demonstrates some protection against oxidative stress in rats with induced diabetes (Amin et al 2006) and the saponins are found to have a hypoglycaemic action.

An in vitro test has also identified COX-2 inhibition activity (Hong et al 2002), suggesting possible anti-inflammatory actions. An animal study using a percolated extract of the fruits of tribulus at a dose of 100 mg/kg showed a significant analgesic effect compared to the control group with a lower gastric ulcerogenecity than indomethacin (Heidari et al 2007).

Two isolated constituents, tribulosin and beta-sitosterol-D-glucoside, have shown anthelmintic activity in vitro against *Caenorhabditis elegans* (Deepak et al 2002).

Of eight steroid saponins tested, two showed potent antifungal activity against *Candida albicans*, with one, TTS-12, demonstrating its ability to decrease virulence and destroy the cell membrane (Zhang et al 2005).

Protection against mercury-induced nephrotoxicity was demonstrated with 7 days administration of tribulus fruit extract (6 mg/kg body weight) in an animal study (Kavitha & Jagadeesan 2006).

CLINICAL USE

Aphrodisiac

The observed pharmacological effects on androgen status provide a theoretical basis for this activity, but little clinical testing has been conducted.

Results from a 2002 animal study have produced positive results suggestive of aphrodisiac activity (Gauthaman et al 2002). The study compared the effects of subcutaneous testosterone, an orally administered tribulus extract containing protodioscin (45% dry weight) or placebo over 8 weeks in castrated rodents. Both testosterone and tribulus treatments significantly improved sexual behaviour compared with controls, although testosterone was the more effective treatment.

A follow-up study by the same research team added further data (Gauthaman et al 2003). In this study, rats were treated with 2.5, 5 and 10 mg/kg once daily for 8 weeks. The results showed a considerable increase in sexual behaviour and slight weight gain compared to controls. Interestingly, the results were more pronounced at the lower dose range.

Despite positive data from animal studies, a recent small controlled clinical trial of tribulus in young men aged between 20 and 36 years showed no statistical increase in testosterone levels in the treated group (Neychev & Mitev 2005). The men were divided into two treatment groups (each n = 7) and one control group (n = 7). One group was given 10 mg/kg and the other 20 mg/kg per day divided into three even doses for 4 weeks. There was no significant change in testosterone, androstenedione or luteinising hormone.

Ergogenic aid

Tribulus has been touted as a natural anabolic supplement or ergogenic aid, capable of producing large gains in strength and lean muscle mass in 5–28 days. The observed pharmacological effects

on androgen status provide a theoretical basis for this activity; however, clinical trials have produced disappointing results.

A small, randomised, placebo-controlled study found that treatment with tribulus (3.21 mg/kg body weight daily) had no effects on body composition and exercise performance in resistance-trained men after 8 weeks (Antonio et al 2000). The study has been criticised by some athletes, as the dose of tribulus tested was very low and not indicative of the doses used in real life. A more recent RCT by Rogerson et al compared the effects of tribulus extract (450 mg/day) to placebo in 22 Australian elite male rugby league players during their preseason training period. The double study was conducted over 5 weeks and found that muscular strength and fat-free mass increased significantly in both groups, with no advantage seen for tribulus treatment. Additionally, no significant differences were seen for urinary testosterone/epitestosterone ratio compared with placebo. Once again, the trial has been criticised as using subtherapeutic doses which do not reflect manufacturer recommendations or current use (Rogerson et al 2007).

Menopausal symptoms

Saponins from tribulus appear to increase FSH in women, which in turn increase levels of oestradiol (Mills & Bone 2000). The primary site of action of steroidal saponins is probably the hypothalamus (Trickey 1998). In postmenopausal women, steroidal saponin-containing herbs like tribulus have been used to alleviate oestrogen withdrawal symptoms. Clinical studies are unavailable to determine whether the effect is significant.

Kidney stones

A human trial was conducted with a herbal combination containing *Tribulus terrestris* and another Ayurvedic herb, *Bergenia ligulata*, in the treatment of 14 patients with renal calculi and 16 patients with ureteric calculi; 28.57% of patients with renal calculi and 75% patients with ureteric calculi passed their calculi completely and in other patients, there was a marked or partial expulsion of calculi along with changes in the shapes and sizes of calculi (Prasad & Bharathi 2007). The role of tribulus in achieving these results is unknown.

OTHER USES

Traditionally, the acidic fruits are thought to be cooling and are used for painful micturition, urinary disorders, kidney stone prevention and impotence, whereas the leaves are thought to possess tonic, diuretic and anti-inflammatory properties and are used to increase menstrual flow. Interestingly, preliminary research into the pharmacological actions of tribulus or its constituents provides some support for several of these uses.

DOSAGE RANGE

In Australia, preparations containing both the fruit and the root are available that are standardised to saponin content. As no clinical studies are available, the manufacturers' recommended dose is included here, which is 2–30 g/day.

- Leaf: 750–1500 mg/day of extract standardised to contain 45% protodioscin.

TOXICITY

Although toxicity levels in humans are not known, extensive grazing on tribulus by sheep produces a syndrome known as 'staggers', which is characterised by nervous and muscular locomotor disturbances (Bourke 1984). Outbreaks are repeatedly associated with drought periods during which sheep graze on large areas of *Tribulus terrestris* for many months at a time (Bourke 1995, Glastonbury et al 1984). Investigation with isolated harmane and norharmane found naturally in tribulus have found these constituents to be responsible for the 'staggers' syndrome (Bourke et al 1992).

Hepatogenous photosensitivity has also been reported among sheep grazing on *Tribulus terrestris* for long periods (Bourke 1984, Glastonbury et al 1984, McDonough et al 1994, Miles et al 1994, Tapia et al 1994, Wilkins et al 1996). A small animal study examined the clinical, laboratory and pathological findings of this disease in sheep and concluded that tribulus was responsible for hepatogenous photosensitivity (Aslani et al 2003). Laboratory and pathology tests found significantly increased white blood cells, bilirubin, total serum protein and plasma fibrinogen, and histological findings showed crystalloid materials in the bile ducts with hepatocyte degeneration. A year later, the same research team found very similar results in goats (Aslani et al 2004).

ADVERSE REACTIONS

Gastrointestinal disturbance may occur in sensitive individuals due to the saponin content.

SIGNIFICANT INTERACTIONS

Controlled studies are not available and currently no interactions are known.

PRACTICE POINTS/PATIENT COUNSELLING

- Tribulus has been used traditionally in various parts of the world to treat colicky spasms, diarrhoea, cardiovascular disease and various kidney disorders, including kidney stones, and as an insect repellent.
- Tribulus has not undergone significant clinical testing, so much information is speculative and based on animal and test tube studies.
- Popular as an aphrodisiac, some research suggests that it increases levels of DHEA, testosterone and NO release, providing a theoretical basis for this activity. Until controlled studies are available, it is uncertain whether these effects are clinically significant.
- Tribulus is also popular among athletes as an ergogenic aid and to increase muscle strength; however, clinical studies using low-dose tribulus have not supported this use. Larger controlled studies testing higher doses that are reflective of real-world use are required to determine its efficacy.

CONTRAINDICATIONS AND PRECAUTIONS

People with androgen-sensitive tumours should avoid use.

PREGNANCY USE

Not to be used in pregnancy.

PATIENTS' FAQs

What will this herb do for me?

Preliminary research suggests that this herb increases androgen levels and improves sexual function, but human studies are not available to confirm these effects.

When will it start to work?

This is unknown.

Are there any safety issues?

Pregnant and lactating women and people with androgen-sensitive tumours should avoid use.

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Turmeric

HISTORICAL NOTE Turmeric is a perennial herb, yielding a rhizome that produces a yellow powder that gives curry its characteristic yellow colour and is used to colour French mustard and the robes of Hindu priests. Turmeric was probably first cultivated as a dye, and then as a condiment and cosmetic. It is often used as an inexpensive substitute for saffron in cooking and in the 13th century Marco Polo marvelled at its similarities to saffron. Both Indian Ayurvedic and Chinese medicines use turmeric for the treatment of inflammatory and digestive disorders and turmeric has also been used in tooth powder or paste. Research has focused on turmeric's antioxidant, hepatoprotective, anti-inflammatory, anticarcinogenic and antimicrobial properties, in addition to its use in cardiovascular disease and gastrointestinal disorders (National Library of Medicine 2001).

COMMON NAME
Turmeric

OTHER NAMES
Chiang-huang, curcuma, curcumae longae rhizoma, curcuma rhizome, e zhu, haridra, Indian saffron, jiang huang, jiang huang curcumae rhizoma, turmeric rhizome, turmeric root, yellow root, yu jin, zedoary

BOTANICAL NAME/FAMILY
Curcuma longa (family Zingiberaceae [ginger])

PLANT PART USED
Dried secondary rhizome (containing not less than 3% curcuminoids calculated as curcumin and not less than 3% volatile oil, calculated on dry-weight basis).

CHEMICAL COMPONENTS
Turmeric rhizome contains 5% phenolic curcuminoids (diarylheptanoids), which give turmeric the yellow colour. The most significant curcuminoid is curcumin (diferuloylmethane).

It also contains up to 5% essential oil, including sesquiterpene (e.g. Zingerberene), sesquiterpene alcohols and ketones, and monoterpenes.

Turmeric also contains immune-stimulating polysaccharides, including acid glucans known as ukonan A, B and C (Evans 2002).

MAIN ACTIONS
Most research has focused on a series of curcumin constituents found in the herb. Many of the animal studies, however, involve parenteral administration and oral curcumin or turmeric is likely to be far less active because curcumin is poorly absorbed by the gastrointestinal tract and only trace amounts appear in the blood after oral intake (Ammon & Wahl 1991). Curcumin may, however, have significant activity in the gastrointestinal tract, and systemic effects may take place as a consequence of local gastrointestinal effects or be associated with metabolites of the curcuminoids.

Antioxidant
Studies have shown that turmeric, as well as curcumin, has significant antioxidant activity (Ak & Gulcin 2008, Bengmark 2006, Menon & Sudheer 2007, Shalini & Srinivas 1987, Soudamini et al 1992). Turmeric not only exerts direct free radical scavenging activity, it also appears to enhance the antioxidant activity of endogenous antioxidants, such as glutathione peroxidase, catalase and quinine reductase. Curcumin has been shown to induce phase II detoxifying enzymes (glutathione peroxidase, glutathione reductase, glucose-6-phosphate dehydrogenase and catalase) (Iqbal et al 2003). Additionally, its antioxidant effects are 10-fold more potent than ascorbic acid or resveratrol (Song et al 2001). In addition to curcumin, turmeric contains the antioxidants protocatechuic acid and ferulic acid and exhibits significant protection to DNA against oxidative damage in vitro (Kumar et al 2006).

Turmeric's antioxidant activity may mediate damage produced by myocardial and cerebral ischaemia (Al-Omar et al 2006, Fiorillo et al 2008, Shukla et al 2008) and diabetes (Farhangkhoee et al 2006, Jain et al 2006; Kowluru & Kanwar 2007). Turmeric has been shown to restore myocardial antioxidant status, inhibit lipid peroxidation and protect against ischaemia–reperfusion-induced myocardial injuries in two animal studies (Fiorillo et al 2008, Mohanty et al 2004). The mechanism is likely due to curcumin's antioxidant and anti-inflammatory effects. Curcumin has also been found to prevent protein glycosylation and lipid peroxidation caused by high glucose levels in vitro (Jain et al 2006) and to improve diabetic nephropathy (Srinivasan 2005) and retinopathy (Kowluru & Kanwar 2007). Turmeric has also been shown to suppress cataract development and collagen cross-linking, promote

wound healing, and lower blood lipids and glucose levels (Jain et al 2006, Panchatcharam et al 2006).

NF-kappa-B inhibition

The many and varied effects of curcumin may be partly associated with the inhibition of transcription factor, nuclear factor-kappa beta (NF-kappa-B), and induction of heat shock proteins. NF-kappa-B is a transcription factor pivotal in the regulation of inflammatory genes and is also closely associated with the heat shock response, which is a cellular defence mechanism that confers broad protection against various cytotoxic stimuli. Inhibition of NF-kappa-B may reduce inflammation and protect cells against damage (Chang 2001) and curcumin has been found to attenuate experimental colitis in animal models through a mechanism correlated with the inhibition of NF-kappa-B (Salh et al 2003). The clinical significance of this is unclear.

Anti-inflammatory

There have been a large number of studies examining the anti-inflammatory effects of curcumin. Turmeric is a dual inhibitor of the arachidonic acid cascade. Curcumin has been shown to exert anti-inflammatory effects via phospholipase, lipo-oxygenase, COX-2, leukotrienes, thromboxane, PGs, NO, collagenase, elastase, hyaluronidase, monocyte chemoattractant protein-1, IFN-inducible protein, TNF and IL-12 (Chainani-Wu 2003, Lantz et al 2005, Rao 2007). Due to its anti-inflammatory effects, curcumin has shown promise in many chronic disorders such as arthritis, colitis, allergies, arteriosclerosis, diabetes, respiratory disorders, hepatic injury, pancreatic disease, intestinal disorders, eye diseases, neurodegenerative diseases and various cancers (Aggarwal et al 2007, Bengmark 2006).

The anti-inflammatory effect of curcumin was tested in adjuvant-induced chronic inflammation rats which found that curcumin significantly reduced C-reactive protein, TNF-alpha, IL-1 and NO, with no significant changes observed in PGE_2 and leukotriene B4 levels or lymphocyte proliferation (Banerjee et al 2003). Curcumin has also been shown to inhibit inflammation in experimental pancreatitis via inhibition of NF-kappa-B and activator protein-1 in two rat models (Gukovsky et al 2003).

Gastrointestinal effects

Hepatoprotective

Extracts of both turmeric and curcumin have been found to prevent and improve carbon tetrachloride-induced liver injury both in vivo and in vitro (Abu-Rizq et al 2008, Deshpande et al 1998, Fu et al 2008, Kang et al 2002, Wu et al 2008), curcumin also protects against dimethylnitrosamine-induced liver injury (Farombi et al 2008), reverses aflatoxin-induced liver damage in experimental animals (Soni et al 1992) and effectively suppresses the hepatic microvascular inflammatory response to lipopolysaccharides in vivo (Lukita-Atmadja et al 2002). An ethanol soluble fraction of turmeric was shown to contain three antioxidant compounds, curcumin, demethoxycurcumin and bisdemethoxycurcumin, which exert similar hepatoprotective activity to silybin and silychristin in vitro (Song et al 2001).

Several different mechanisms may contribute to turmeric's hepatoprotective activity. Curcumin has been shown to prevent lipoperoxidation of subcellular membranes in a dosage-dependent manner, due to an antioxidant mechanism (Quiles et al 1998) and turmeric may also protect the liver via inhibition of NF-kappa-B (see above), which has been implicated in the pathogenesis of alcoholic liver disease. Curcumin also appears to chelate hepatic and serum iron in vivo (Jiao et al 2006, 2008). Iron is pro-oxidant to the liver, which may be problematic during hepatic disease. Recent research also suggests that curcumin may be useful in preventing hepatic fibrosis caused by chronic liver disease (Fu et al 2008, O'Connell & Rushworth 2008). Curcumin also blocked endotoxin-mediated activation of NF-kappa-B and suppressed the expression of cytokines, chemokines, COX-2 and iNOS in Kupffer cells (Nanji et al 2003).

Cholagogue and hypolipidaemic

Turmeric extract or curcumin extract has shown dose-dependent hypolipidaemic activity in vivo (Asai & Miyazawa 2001, Babu & Srinivasan 1997, Keshavarz 1976, Manjunatha & Srinivasan 2007a, 2007b, Ramirez-Tortosa et al 1999, Soudamini et al 1992). One in vivo study suggests that curcumin may stimulate the conversion of cholesterol into bile acids, and therefore increase the excretion of cholesterol (Srinivasan & Sambaiah 1991). A further study demonstrated that supplementation with turmeric reduces fatty streak development and oxidative stress (Quiles et al 2002). Curcumin also increases LDL receptor mRNA (Peschel et al 2007). Oral curcumin has also been shown to stimulate contraction of the gall bladder and promote the flow of bile in healthy subjects (Rasyid & Lelo 1999).

Antispasmodic

Curcuminoids exhibit smooth muscle relaxant activity possibly mediated through calcium channel blockade, although additional mechanisms cannot be ruled out (Gilani et al 2005). Curcuminoids produced antispasmodic effects on isolated guinea pig ileum and rat uterus by receptor-dependent and independent mechanisms (Itthipanichpong et al 2003).

Cancer

Curcumin has been studied for its wide-ranging effects on tumorigenesis, angiogenesis, apoptosis and signal transduction pathways (Gururaj et al 2002, Mohan et al 2000, Thaloor et al 1998). It is known to inhibit oncogenesis during both the promotion and the progression periods in a variety of cancers (Anto et al 1996, Kuttan et al 1985, Menon et al 1999, Ruby et al 1995). Curcumin was found to possess chemopreventive effects against skin cancer, stomach cancer, colon cancer, prostate cancer, breast cancer and oral cancer in mice.

Chemoprevention

Chemoprevention refers to reversing, suppressing or preventing the process of carcinogenesis. Carcinogenesis results from the accumulation of multiple sequential mutations and alterations in nuclear and cytoplasmic molecules, culminating in invasive neoplasms. These events have traditionally been separated into three phases: initiation, promotion and progression. Typically, initiation is rapid, whereas promotion and progression can take many years. Ultimately, chemoprevention aims at preventing the growth and survival of cells already committed to becoming malignant (Gescher et al 1998, 2001).

Curcumin inhibits the invasion, proliferation and metastasis of various cancers in vivo (Kunnumakkara et al 2008). Curcumin has been found to effectively block carcinogen-induced skin (Azuine & Bhide 1992), colon (Rao et al 1995a, 1995b, 1995c, 1999) and liver (Chuang et al 2000) carcinogenesis in animals. It has been suggested that the chemoprotective activity of curcumin occurs via changes in enzymes involved in both carcinogen bioactivation and oestrogen metabolism. This is supported by the findings that curcumin treatment produced changes in CYP1A, CYP3A and GST in mice (Valentine et al 2006) and alleviated the CCl_4-induced inactivation of CYPs 1A, 2B, 2C and 3A isozymes in rats, possibly through its antioxidant properties, without inducing hepatic CYPs (Sugiyama et al 2006).

Oral curcumin inhibited chemically induced skin carcinogenesis in mice (Huang et al 1992) and curcumin prevented radiation-induced mammary and pituitary tumours in rats (Inano & Onoda 2002). Curcumin and genistein (from soybeans) inhibited the growth of oestrogen-positive human breast MCF-7 cells induced individually or by a mixture of the pesticides endosulfane, dichlorodiphenyltrichloroethane (DDT) and chlordane, or 17-beta oestradiol (Verma et al 1997). Another study found that curcumin inhibited breast cancer metastases in immunodeficient animals (Bachmeier et al 2007). This may be due to curcumin's ability to reduce NF-kappa-B and therefore downregulate the two inflammatory cytokines CXCL1 and -2 (Bachmeier et al 2008).

Apoptosis

Apoptosis (programmed cell death) plays a crucial role in regulating cell numbers by eliminating damaged or cancerous cells. Curcumin has been shown to induce apoptosis in many different cancer cell lines, including breast, leukaemia, lymphoma, melanoma, ovarian, colorectal, lung and pancreatic in vitro (Kim et al 2001, Kuo et al 1996, Li et al 2007, Lin et al 2007, Lev-Ari et al 2006, Marin et al 2007, Skommer et al 2007, 2006, Tian et al 2008). Curcumin has also increased apoptosis in breast and ovarian cancers in vivo (Bachmeier et al 2007, Lin et al 2007). Curcumin has been demonstrated to induce apoptosis in human basal cell carcinoma cells associated with the p53 signalling pathway, which controls intracellular redox status, levels of oxidation-damaged DNA and oxidative stress-induced apoptosis (Jee et al 1998). Curcumin has also been found to induce apoptosis in human mutant p53 melanoma cell lines and block the NF-kappa-B cell survival pathway and suppress the apoptotic inhibitor known as XIAP. Because melanoma cells with mutant p53 are strongly resistant to conventional chemotherapy, curcumin may overcome the chemoresistance of these cells and provide potential new avenues for treatment (Bush et al 2001).

Curcumin has also been found to inhibit prostate cancer cell growth in mice (Dorai et al 2001) and decrease proliferation and induce apoptosis in androgen-dependent and androgen-independent prostate cancer cells in vitro. This was found to be mediated through modulation of apoptosis suppressor proteins and interference with growth factor receptor signalling pathways (Dorai et al 2000). In a further study with rats, however, curcumin did not prevent prostate carcinogenesis (Imaida et al 2001).

Antiproliferative

Reduction in proliferation and/or increased apoptosis will lead to tumour regression; however, a more potent effect will be achieved if the two mechanisms occur simultaneously. Curcumin has been shown to do this. The inhibition of cell proliferation is partly related to inhibition of various kinases, such as protein kinase and phosphorylase kinase (Reddy & Aggarwal 1994), and inhibition of several oncogenes and transcription factors. For example, turmeric inhibited epidermal growth factor receptor (EGF-R) signalling via multiple mechanisms, including downregulation of the EGF-R protein, inhibition of intrinsic EGF-R tyrosine kinase activity and inhibition of ligand-induced activation of the EGF-R (Dorai et al 2000). These mechanisms may be particularly important in preventing prostate cancer cells from progressing to a hormone refractory state (Dorai et al 2000). Curcumin has also been found to suppress the growth of multiple breast cancer cell lines and deplete p185neu, the protein product of the HER2/neu proto-oncogene that is thought to be important in human carcinogenesis (Hong et al 1999).

Antimetastatic

Curcumin demonstrated the ability to reduce lung metastases from melanoma cells in mice. The activity of curcumin is varied.

- In cell adhesion assays, curcumin-treated cells showed a dose-dependent reduction in their binding to four extracellular matrix proteins (binding to proteins is associated with the spreading of the cancer). Another study found that curcumin effectively suppressed COX-2, vascular endothelial growth factor and intercellular adhesion molecules, whilst enhancing the expression of antimetastatic proteins, tissue inhibitor metalloproteases-2, non-metastatic gene 23 and E-cadherin a transmembrane protein that plays an important role in cell adhesion (Kuttan et al 2007).
- Curcumin-treated cells showed a marked reduction in the expression of integrin receptors (integrins functionally connect the cell interior with the extracellular matrix, another process necessary for metastases).

Chemotherapy

Curcumin enhanced the cytotoxicity of chemotherapeutic agents in prostate cancer cells in vitro by inducing the expression of certain androgen receptor and transcription factors and suppressing NF-kappa-B activation (Hour et al 2002). Curcumin enhanced the antitumour effect of cisplatin against fibrosarcoma (Navis et al 1999), fluorouracil and oxaliplatin in colorectal cancer (Du et al 2006, Li et al 2007) and gemcitabine and paclitaxel in bladder cancer (Kamat et al 2007). Curcumin also attenuated multidrug resistance in a non-small cell lung cancer cell line (Andjelkovic et al 2008) and acted as a radiosensitiser for cervical cancer in vitro (Javvadi et al 2008).

Curcumin, however, was found to significantly inhibit cyclophosphamide-induced tumour regression in an in vivo model of human breast cancer. It is suspected that this occurred as a result of inhibition of free radical generation and blockade of JNK function. As such, curcumin intake should be limited in people undergoing treatment for breast cancer with cyclophosphamide until further investigation can clarify the significance of these findings (Somasundaram et al 2002).

Immunomodulation

Curcumin administration was found to significantly increase the total white blood cell count and circulating antibodies in mice. A significant increase in macrophage phagocytic activity was also observed in curcumin-treated animals (Antony et al 1999). However, curcumin has also been demonstrated to have some immunosuppressive activity. Curcumin inhibits PAR2- and PAR4-mediated human mast cell activation by blocking the ERK pathway (Baek et al 2003).

An in vivo study using a cardiac transplant model found that curcumin also significantly reduced expression of IL-2, IFN-gamma and granzyme B (a serine protease associated with the activity of killer T-lymphocytes and NK cells) and increased mean survival time. Curcumin was further shown to work synergistically with the antirejection drug, cyclosporine (Chueh et al 2003).

Curcumin also modulates other interleukins and has been shown in vitro to be a potent inhibitor of the production of the pro-inflammatory cytokine IL-8, thereby reducing tumour growth and carcinoma cell viability. Curcumin not only inhibited IL-8 production but also inhibited signal transduction through IL-8 receptors (Hidaka et al 2002) and to inhibit cell proliferation, cell-mediated cytotoxicity and cytokine production most likely by inhibiting NF-kappa-B target genes (Gao et al 2004).

Cardiovascular effects

Antiplatelet

Curcumin has been shown to inhibit platelet aggregation in vivo (Chen et al 2007, Srivastava et al 1985, 1986) and in vitro (Jantan et al 2008, Srivastava 1989, Srivastava et al 1995). The anticoagulant effect of curcumin is weaker than that of aspirin, which is four-fold more potent than curcumin in treatment of collagen- and noradrenalin-induced thrombosis. Curcumin 100 mg/kg and aspirin 25 mg/kg resulted in 60% protection from thrombosis (Srivastava et al 1985).

Anti-atherogenic

A hydro-ethanolic extract of turmeric was found to decrease LDL oxidation, have a vitamin E-sparing effect and lower the oxidation of erythrocyte and liver membranes in rabbits fed a diet high in saturated fat and cholesterol (Mesa et al 2003, Ramirez-Tortosa et al 1999). The atheroscleroprotective potential of turmeric was further demonstrated by an animal study that found turmeric lowered blood pressure and reduced the atherogenic properties of cholesterol (Zahid Ashraf et al 2005). Curcumin also inhibits the proliferation and migration of vascular smooth muscle cells in vitro (Yang et al 2006).

Many in vivo studies have investigated the effects of dietary curcumin on blood cholesterol in diabetic animals (Babu & Srinivasan 1997, Manjunatha & Srinivasan 2007a, 2007b, Pari & Murugan 2007). The two Manjunatha and Srinivasan studies found that curcumin significantly lowered plasma cholesterol but only lowered hepatic cholesterol in animals with normal baseline cholesterol. Additionally, hepatic alpha-tocopherol and glutathione levels and serum glutathione peroxidase and glutathione transferase were increased. Babu and Srinivasan also found a significant decrease in blood triglyceride and phospholipid levels (Babu & Srinivasan 1997). In a parallel study in which diabetic animals were maintained on a high cholesterol diet, curcumin lowered cholesterol and phospholipid and countered the elevated liver and renal cholesterol and triglyceride levels seen in the diabetic animals (Babu & Srinivasan 1997).

Wound healing

Wound healing is a highly ordered process, requiring complex and coordinated interactions involving peptide growth factors, of which transforming growth factor-beta (TGF-beta) is one of the most important. Nitric oxide is also an important factor in healing, and its production is regulated by iNOS. Topical application of curcumin accelerated wound healing in normal and diabetic rats. The wound healing is partly associated with the regulation of the growth factor TGF-beta-1 and iNOS (Mani et al 2002). Curcumin's wound healing ability has been confirmed in several other animal studies (Sidhu et al 1998, 1999). Wounds of animals treated with curcumin showed earlier re-epithelialisation, improved neovascularisation, increased migration of various cells, including dermal myofibroblasts, fibroblasts and macrophages into the wound bed, and a higher collagen content (Sidhu et al 1999). It appears to be effective when used orally or as a local application.

Curcumin has also demonstrated powerful inhibition against hydrogen peroxide damage in human keratinocytes and fibroblasts (Phan et al 2001) and pretreatment with curcumin significantly enhanced the rate of wound contraction, decreased mean wound healing time, increased synthesis of collagen, hexosamine, DNA and NO and improved

fibroblast and vascular densities in full thickness wounds in mice exposed to whole-body gamma-radiation (Jagetia & Rajanikant 2004).

Antimicrobial

Turmeric is used as an antimicrobial for preserving food (Jayaprakasha et al 2005) and has been found to have antifungal activity, as well as inhibiting aspergillus growth and aflatoxin production in feeds (Gowda et al 2004).

Curcumin has also been found to have dose-dependent, antiprotozoan activity against *Giardia lamblia* with inhibition of parasite growth and adherent capacity, induction of morphological alterations and apoptosis-like changes in vitro (Perez-Arriaga et al 2006). Curcumin has also shown in vitro and in vivo activity against malaria, with inhibition of growth of chloroquine-resistant *Plasmodium falciparum* in vitro and enhancement of survival in mice infected with *P. berghei* (Reddy et al 2005).

Psoriasis

Topical curcumin reduced the severity of active, untreated psoriasis as assessed by clinical, histological and immunohistochemical criteria in an observational study of 10 patients. Curcumin was also found to decrease phosphorylase kinase, which is involved in signalling pathways, including those involved with cell migration and proliferation (Heng et al 2000). Topical administration of curcumin also induced normal skin formation in the modified mouse tail test (Bosman 1994). The effects are thought to be due to immune-modulating, anti-inflammatory and cyclo-oxygenase inhibitory actions. The downregulation of pro-inflammatory cytokines supports the view that turmeric antioxidants may exert a favourable effect on psoriasis-linked inflammation. Moreover, because IL-6 and IL-8 are growth factors for keratinocytes, their inhibition by those antioxidants may reduce psoriasis-related keratinocyte hyperproliferation (Miquel et al 2002).

OTHER ACTIONS

Curcumin's anti-inflammatory and antioxidant actions may be useful in preventing neurodegenerative diseases, such as Alzheimer's dementia and Parkinson's disease, and curcumin has been found to target multiple pathogenic cascades in preclinical models (transgenic and amyloid infusion models) of AD (Cole et al 2005, Calabrese et al 2006). Curcumin has also been found to dose-dependently inhibit neuroglial proliferation, with low doses being as effective as higher doses given a longer period of treatment (Ambegaokar et al 2003). It may also enhance immune clearance of amyloidosis in the brain (Zhang et al 2006).

Curcumin had anti-asthmatic activity in animal models of induced asthma. Curcumin (20 mg/kg body weight) treatment significantly inhibited chemical (ovalbumin)-induced airway constriction and airway hyperreactivity. The results demonstrate that curcumin is effective in improving the impaired airways features in ovalbumin-sensitised guinea pigs (Ram et al 2003).

Curcumin has been found to have inhibitory effects on P-glycoprotein in numerous test tube studies (Anuchapreeda et al 2002, Limtrakul et al 2004, Nabekura et al 2005). The clinical significance of this observation has yet to be determined.

CLINICAL USE

In practice, turmeric and the various curcuminoids are used in many forms and administered via various routes. This review will focus mostly on those methods of use that are commonly used and preparations that are available over the counter (OTC), such as oral dose forms and topical applications.

Cancer

Epidemiological data suggest that curcumin reduces the rate of colorectal cancer (Hergenhahn et al 2002) and curcumin has wide-ranging chemopreventive activity in preclinical carcinogenic models (Plummer et al 2001), most notably for gastrointestinal cancers (Ireson et al 2001). To date, however, there are no controlled trials to attest to turmeric's efficacy in cancer treatment or prevention.

Curcumin appears to be a well-tolerated adjunctive treatment option for patients with pancreatic cancer. Twenty-five participants took 8 g of curcumin daily. Despite significant inter-patient variations in blood curcumin levels, NF-kappa-B, COX-2 and phosphorylated signal transducer and activator of transcription 3 were all downregulated in peripheral blood mononuclear cells (Dhillon et al 2008).

In a phase 1 study, curcumin taken orally for 3 months at a starting dose of 500 mg/day was found to produce histologic improvement in cases of bladder cancer, oral leucoplakia, intestinal metaplasia of the stomach, cervical intraepithelial neoplasm and Bowen's disease (Cheng et al 2001).

An ethanol extract of turmeric, as well as an ointment of curcumin, was found to produce remarkable symptomatic relief in patients with external cancerous lesions (Kuttan et al 1987) and there are clinical reports to suggest that curcumin could be safe and effective in the treatment of idiopathic inflammatory orbital pseudotumours (Lal et al 2000).

Dyspepsia/peptic ulcers

A randomised, controlled, double-blind, prospective, multicentre pilot study compared the effects of dried extracts of greater celandine and turmeric with placebo in 76 patients with colicky abdominal pain in the right upper quadrant due to biliary dyskinesia. Abdominal pain was reduced more quickly with active treatment; however, other symptoms such as fullness, nausea and vomiting did not respond (Niederau & Gopfert 1999). Another randomised, placebo-controlled, double-blind study that investigated the efficacy of turmeric for treatment of dyspepsia and flatulence in 116 adult patients with acidic dyspepsia, flatulent dyspepsia or atonic dyspepsia found that 87% of patients receiving turmeric responded compared to 53% receiving placebo (Thamlikitkul et al 1989).

In a study of 24 patients with duodenal or gastric ulcers varying between 0.5 and 1.5 cm in diameter, 300 mg of turmeric given five times daily, 30–60 min before meals, at 4 pm and at bedtime successfully healed 48% of ulcers after 4 weeks and 76% after 12 weeks. Of 20 patients who had erosion gastritis and dyspepsia, the same treatment produced a satisfactory reduction in abdominal pain and discomfort after the first and second week (Prucksunand et al 2001). Turmeric has also been positively compared to a liquid antacid for the treatment of gastric ulcer in a controlled clinical trial (Kositchaiwat et al 1993).

Irritable bowel disease (IBD)

Turmeric extract shows promise in the symptomatic treatment of IBD, according to a partially blinded, randomised study by Bundy et al (2004). The study of 207 volunteers with diagnosed irritable bowel syndrome (IBS) complying with the Rome II criteria were randomly assigned to receive either 72 mg or 144 mg of turmeric a day or placebo for 8 weeks (Bundy et al 2004). The group receiving the lower dose (72 mg/day) experienced a significant 53% decrease in irritable bowel symptoms, whereas higher treatment (144 mg/day) resulted in a 60% decrease when compared to placebo ($P < 0.001$). Abdominal discomfort was also reduced by 22% and 25% of patients in the 72 mg and 144 mg groups, respectively ($P < 0.001$). Approximately two-thirds of the participants in the active groups reported overall symptom improvement and had better quality-of-life scores.

Inflammatory bowel disease

An open-label pilot study has produced preliminary data to suggest that curcumin may be effective in inflammatory bowel disease (Holt et al 2005). Five patients with Crohn's disease received 360 mg of curcumin 3 times a day for 1 month, followed by 4 times a day for another 2 months. The Crohn's disease activity index (CDAI), C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) fell significantly in 4 out of 5 patients. Five patients with ulcerative proctitis were also enrolled and received 550 mg of curcumin twice a day for 1 month, then three times a day for another month. Overall, stool quality was greatly improved and frequency was significantly reduced. Two patients were able to eliminate their concomitant medications altogether, whilst another two patients were able to reduce them. The CRP and ESR also returned to within normal limits by the cessation of the study.

A randomised, double-blind, multicentre trial of 89 patients examined the efficacy of curcumin as a maintenance therapy in ulcerative colitis (Hanai et al 2006). Patients in the active group received 1 g of curcumin, twice a day with sulfasalazine or mesalazine as compared to placebo plus sulfasalazine or mesalazine. At the end of the study period, 4.65% of patients in the curcumin group relapsed during treatment as compared to 20.51% in the placebo group ($P = 0.040$). The clinical activity index ($P = 0.038$) and endoscopic index ($P = 0.0001$) were also significantly improved. This is a promising result that may have great clinical significance.

Hyperlipidaemia

Turmeric may be associated with a decrease in the risk of cardiovascular disease and an intake of 200 mg of a hydro-ethanolic extract of turmeric may decrease total blood lipid peroxides and HDL- and LDL-lipid peroxidation, as well as normalise plasma fibrinogen levels and apolipoprotein B/apolipoprotein A ratio (Miquel et al 2002).

A placebo-controlled, randomised, double-blind study investigated the effects of curcumin on the serum lipids in 36 elderly men and women (Baum et al 2007). The participants were randomised to either receive 4 g/day of curcumin, 1 g/day of curcumin or placebo for 6 months. Neither active product significantly altered triacylglycerols or cholesterol at 1 nor 6 months; however, the concentrations of plasma curcumin and serum cholesterol were positively and significantly correlated. This appears to indicate that curcumin may be a mild hypocholesterolaemic agent; however, larger trials are needed.

In an open trial, 10 healthy volunteers received 500 mg/day of curcumin for 7 days. A significant decrease in the level of serum lipid peroxides (33%), increase in HDL cholesterol (29%) and a decrease in total serum cholesterol (11.63%) were noted. It also reduced serum lipid peroxides (Soni & Kuttan 1992). In a subsequent study, a 45-day intake (by healthy individuals 27–67 years of age) of a turmeric hydro-alcoholic extract at a daily dose equivalent to 20 mg of curcumin resulted in a significant decrease in serum lipid peroxides (Ramirez-Bosca et al 1995). A daily intake of turmeric equivalent to 20 mg of the phenolic antioxidant curcumin for 60 days also decreased peroxidation of both HDL and LDL in 30 healthy volunteers ranging in age from 40 to 90 years. The effect was quite striking in the persons with high baseline values of peroxidised compounds in these lipoproteins, although no apparent change took place in the persons having low baseline values (Ramirez et al 1997).

Psoriasis

A phase 2, non-blinded, open-label trial investigated the effect of curcuminoid C3 complex (500 mg, 3 capsules 3 times a day) in 12 patients with plaque psoriasis for 12 weeks followed by a 4-week observation period (Kurd et al 2008). Results were poor with the intention-to-treat analysis response rate only reaching 16.7%. Of the eight patients who completed the trial the two participants who responded achieved good results (83% and 88% improvement in symptoms), however this could be due to a placebo effect. Overall, the medication was well tolerated with only mild side effects being reported, due to either gastrointestinal upset or hot flushing.

Arthritis

In a randomised, controlled double-blind study, curcumin 1200 mg/day was compared with phenylbutazone in subjects with rheumatoid arthritis

(RA). Curcumin was found to be effective in improving morning stiffness, walking time and joint swelling; however, the effects of phenylbutazone were stronger (Deodhar et al 1980).

Curcumin combined with Boswellia, Withania and zinc produced a significant drop in pain and disability in osteoarthritis (OA) of the knee in a randomised, double-blind, placebo-controlled crossover study of 42 patients (Kulkarni et al 1991); however, the contribution of curcumin to these results is unknown.

OTHER USES

Chronic anterior uveitis

An open study of 32 patients found that orally administered curcumin improved symptoms and reduced recurrences of chronic anterior uveitis (a condition often associated with other autoimmune disorders) with an efficacy comparable to corticosteroid therapy, yet without significant side effects (Lal et al 1999).

Oral submucous fibrosis

Turmeric extract 3 g, oil 600 mg and oleoresin 600 mg effectively relieved symptoms and reduced the number of micronuclei (a sign of damage to the DNA and chromosomal integrity) in circulating lymphocytes and oral mucosal cells in patients with oral submucous fibrosis, a debilitating disease of the oral cavity mainly caused by chewing betel nut or tobacco (Hastak et al 1997).

DOSAGE RANGE

Internal use

- Powdered turmeric: 1.5–3 g/day in water or cooking.
- Liquid extract (1:1) in 45% ethanol: 5–15 mL/day.
- Powdered extract standardised to 95% curcumin: 100–300 mg/day. Higher doses used for arthritis and cancer.

External use

- Turmeric powder of standardised powdered extract applied as a paste or poultice — half cup of turmeric combined with 1 teaspoon of carbonate of soda and then mixed with hot water to make a paste; spread on gauze and apply to affected area.

ADVERSE REACTIONS

The safety of curcumin is demonstrated by the fact that it has been consumed for centuries at levels of up to 10 mg/day by people in certain countries (Ammon & Wahl 1991). Curcumin was not toxic to humans in doses up to 8000 mg/day when taken by mouth for 3 months (Cheng et al 2001). Multiple other human trials have also found it to be safe with no alteration of liver or renal function tests (Chainani-Wu 2003, Prucksunand et al 2001, Ramirez-Bosca et al 1995, Ramirez et al 1997, Sharma et al 2001).

Large doses of turmeric powder may cause gastrointestinal irritation in some persons (Shankar et al 1980) and very high dosages have been shown to reduce fertility in male rats (human equivalent doses would be 35 g turmeric/70 kg adult) (Bhagat & Purohit 2001). Normal therapeutic dosages of turmeric are not expected to affect fertility. Contact dermatitis has been reported (Hata et al 1997), as has a single case of anaphylaxis (Robinson 2003).

SIGNIFICANT INTERACTIONS

Controlled studies are not available, so interactions are based on evidence of activity and are largely theoretical and speculative.

Antiplatelet drugs

Turmeric has a theoretical interaction with antiplatelet drugs; antiplatelet properties have been demonstrated for curcumin, therefore it may produce an additive effect. The clinical significance of this interaction is unclear and likely to be dose-dependent.

Anticoagulants

Theoretically, high-dose turmeric preparations may increase the risk of bleeding when used together with anticoagulant drugs — caution is advised.

Cyclophosphamide

Animal studies suggest that curcumin may reduce drug efficacy — avoid.

CONTRAINDICATIONS AND PRECAUTIONS

Turmeric is contraindicated in bile duct obstruction (Blumenthal et al 2000) and high doses are probably best avoided in males and females wanting to conceive.

Curcumin is also contraindicated in breast cancer patients treated with cyclophosphamide until the significance of an in vivo model of breast cancer, which found that curcumin reduced the tumour regression effects of chemotherapy, is clarified (Somasundaram et al 2002).

Due to antiplatelet activity and possible increased risk of bleeding, use of concentrated extracts should be suspended 1 week prior to major surgery; however, usual dietary intakes are likely to be safe.

PREGNANCY AND LACTATION USE

When used as a spice, this herb is most likely to be safe; however, the safety of therapeutic doses has not been established. Turmeric has been demonstrated not to be mutagenic in vitro (Nagabhushan & Bhide 1986) or to be teratogenic in mice (Garg 1974, Vijayalaxmi 1980). Constituents and/or metabolites of turmeric and curcumin were transferred to suckling pups, but no ill effect on the offspring was reported.

PATIENTS' FAQs

What will this herb do for me?

In countries where people use turmeric extensively in cooking (generally in curries), the intake seems to be associated with a lower level of certain chronic conditions, possibly including cancer, gastrointestinal diseases and arthritis. There have been some encouraging studies supporting this.

When will it start to work?

In some studies, the effect began to be noticed after 2 weeks. However, as most of the conditions where turmeric may be beneficial are chronic in nature, treatment with turmeric should be considered long term.

Are there any safety issues?

Turmeric is considered very safe at normal dietary or therapeutic dosages with turmeric extracts. High doses are generally not recommended during pregnancy or for those wanting to conceive.

PRACTICE POINTS/PATIENT COUNSELLING

- In Ayurvedic medicine, turmeric is used to strengthen the overall energy of the body, relieve gas, dispel worms, improve digestion, regulate menstruation, dissolve gallstones, relieve arthritis and purify the blood (Blumenthal et al 2000).
- In Traditional Chinese medicine (TCM), turmeric is used for bruises, sores, ringworm, chest pain, toothache and jaundice. Turmeric was also recommended for abdominal pain, mass formation in the abdomen and amenorrhoea (Blumenthal et al 2000).
- Turmeric is commonly used in foods and is likely to be a safe and healthy addition to the diet.
- Turmeric has been shown to have antioxidant, anti-inflammatory and anti-atherosclerotic activities; however, further clinical evidence is needed before it can be recommended to treat specific conditions.
- Clinical evidence suggests that turmeric may provide benefit for people with dyspepsia, peptic ulcer, hyperlipidaemia and arthritis and there is emerging evidence to suggest that turmeric may help prevent a number of cancers as well as being useful as an adjuvant in cancer treatment.

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Tyrosine

HISTORICAL NOTE Tyrosine has been used by the military in the USA and the Netherlands to counter the stressful effects of cold, prolonged and excessive physical activity. It also appears to improve cognition and performance in soldiers under psychologically stressful conditions and has been scientifically shown to improve physical and mental endurance (Deijen et al 1999).

BACKGROUND AND RELEVANT PHARMACOKINETICS

Tyrosine is a conditionally essential aromatic amino acid. It can be taken through the diet or synthesised in the body from phenylalanine, except in phenylketonurics. L-Tyrosine is absorbed in the small intestine by active transport and transported to the liver where it is involved in a number of biochemical reactions, such as protein synthesis and oxidative catabolic reactions. L-Tyrosine that is not metabolised in the liver is distributed via the systemic circulation to various tissues in the body where it is involved in the synthesis of a number of catecholamines and hormones (Hendler & Rorvick 2001), incorporated into protein structures or deaminated for gluconeogenesis. Peak plasma tyrosine

levels occur 2 hours after administration and remain elevated for 6–8 hours (Glaeser et al 1979).

There is some question as to tyrosine's ability to cross the blood–brain barrier and this may explain some of the negative results demonstrated in clinical trials. Proper flow is dependent upon the ratio of tyrosine to other large neutral amino acids (phenylalanine, tryptophan, methionine, leucine, isoleucine and valine) that compete for uptake by neurons (Glaeser et al 1979). A rat study has demonstrated that combining the essential fatty acid alpha-linolenic acid with L-tyrosine, via a special bond, produces an active biological molecule with potent dopaminergic activity, suggesting that alpha-linolenic acid may play a dual role as a carrier for tyrosine and as a membrane- and receptor-improving agent (Yehuda 2002).

CHEMICAL COMPONENTS

L-Tyrosine is the form generally used. Tyrosine is also known as beta-(para-hydroxyphenyl) alanine, alpha-amino-para-hydroxyhydrocinnamic acid and *(S)*-alpha-amino-4-hydroxybenzenepropanoic acid.

FOOD SOURCES

Good dietary sources include soy products, chicken, fish, almonds, avocados, bananas, dairy products, meat, eggs, nuts, beans, oats, wheat, lima beans, pumpkin seeds, sesame seeds and fermented foods such as yoghurt and miso.

DEFICIENCY SIGNS AND SYMPTOMS

The following have been associated with low levels of tyrosine:

- depression
- low blood pressure
- low body temperature
- restless legs syndrome
- hypothyroidism.

MAIN ACTIONS

Neurotransmitter and hormone production

Many of the pharmacological actions of tyrosine relate to its role as a precursor for a number of neurotransmitters and hormones.

Elevating tyrosine concentrations in brain catecholamine neurons (particularly dopamine and noradrenaline neurons) can stimulate neurotransmitter production in actively firing neurons but not in those that are quiescent or firing slowly (Fernstrom 2000).

It plays an essential role in the body as a precursor to the catecholamine neurotransmitters as illustrated below.

Phenylalanine → **Tyrosine** → L-Dopa → Dopamine → Noradrenaline → Adrenaline

Folate, vitamins B3, B6, B12 and C, iron, copper and other nutrients are required for the metabolism of tyrosine to catecholamines.

Thyroid hormones

As tyrosine is a precursor for the synthesis of thyroid hormones it is involved in the regulation of basal metabolic rate, oxygen use, cellular metabolism, growth and development (Tortora & Grabowski 1996).

Tyrosine undergoes iodination to form T_1 (mono-iodotyrosine), a second iodination produces T_2 (di-iodotyrosine) and these combine to produce the active thyroid hormones known as T_3 (tri-iodothyronine) and T_4 (tetra-iodothyronine or thyroxine) (Tortora & Grabowski 1996).

Tyrosine is also involved in the production of other compounds such as melanin, enkephalins and some types of oestrogen (Haas 1992, Tortora & Grabowski 1996).

Antioxidant

L-Tyrosine, a monophenolic amino acid, demonstrates antioxidant activity in various assays including: DPPH (1,1-diphenyl-2-picryl-hydrazyl) free radical scavenging, ABTS (2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) radical scavenging, superoxide anion radical scavenging, hydrogen peroxide scavenging, total ferric ions reducing power and metal chelating on ferrous ions' activities, as well as inhibition of lipid peroxidation of linoleic acid emulsion (Gulcin 2007).

CLINICAL USE

Phenylketonuria

In phenylketonuria (PKU) a severe deficiency of phenylalanine hydroxylase prevents the conversion of phenylalanine to tyrosine resulting in a buildup of phenylalanine which may cause severe mental retardation and a deficiency of tyrosine. PKU is treated by restricting dietary intake of natural protein and substituting a protein source that lacks phenylalanine but is fortified with tyrosine. Unfortunately, free tyrosine supplementation has not been shown to consistently improve neuropsychologic function in PKU, which is possibly because tyrosine levels naturally fluctuate through the day and increases in plasma tyrosine levels are not sustained, so brain influx remains suboptimal despite tyrosine supplementation (Kalsner et al 2001). In practice, plasma tyrosine levels need to be monitored for diurnal variation (normal: 45 micromol/L) and biochemical evidence of tyrosine deficiency should be established before tyrosine supplementation is considered (Poustie & Rutherford 2000, van Spronsen et al 2001).

Enhanced cognition

Therapeutically, tyrosine supplements are used to enhance levels of its derivatives and, therefore, improve cognitive function.

One randomised, placebo-controlled study investigated the effects of L-tyrosine (150 mg/kg) on cognitive performance following one night's sleep loss. Supplementation was found to significantly reduce performance decline, with cognitive improvements lasting approximately 3 hours (Neri et al 1995).

RCTs comparing the effects of a balanced amino acid drink with one lacking in tyrosine and phenylalanine demonstrated that tyrosine-depleted individuals experienced impaired spatial recognition memory and spatial working memory and an increase in plasma prolactin levels (Harmer et al 2001, McTavish et al 2005), indicating a decrease in dopamine neurotransmission within the hypothalamus. Although ratings of depression and other aspects of cognitive function were unaffected, subjective feedback indicated that the participants felt better on the balanced drink (Harmer et al 2001).

Changes in tyrosine transport may also influence cognitive functioning in schizophrenia via the dopamine system (Wiesel et al 2005).

Depression

As tyrosine is a precursor to both dopamine and noradrenaline, researchers have suggested that tyrosine depletion may play a role in the pathogenesis of depression. To date studies testing this hypothesis have produced mixed results. One study found that tyrosine- and phenylalanine-depleted individuals became less content and more apathetic than those given a balanced amino acid mixture (McLean et al 2004). However, a separate study in individuals with a past history of recurrent depression found that tyrosine depletion did not alter objective or subjective measures of mood (McTavish et al 2005), although plasma prolactin levels did increase and performance on a spatial recognition memory task was impaired (McTavish et al 2005). A prospective, randomised, double-blind, placebo controlled trial of 65 subjects with major depression comparing L-tyrosine (100 mg/kg/day), imipramine (2.5 mg/kg/day) or placebo for 4 weeks failed to confirm an antidepressant effect for tyrosine (Gelenberg et al 1990).

Tyrosine may be useful in treating depression associated with a lack of noradrenaline or dopamine. One study involving patients with signs of dopamine-dependent depression (DDD) found that treatment with oral tyrosine (3200 mg/day) caused an immediate improvement in mood, as judged by clinical impression and objective test scores (Montgomery–Asperg Depression Rating Scale) and sleep parameters from day 1 of treatment (Mouret et al 1988a). It has been suggested that a subset of depression patients who fail to respond to antidepressant treatments except amphetamines may be candidates for treatment (L-Tyrosine 2007).

Attention deficit disorder

An 8-week open trial of L-tyrosine in 12 adults with attention deficit disorder (residual type) demonstrated benefits at 2 weeks, however tolerance developed after 6 weeks rendering the treatment ineffectual (Reimherr et al 1987). Previous studies had reported similar effects (Wood et al 1985).

Reward deficiency syndrome

Tyrosine depletion appears to affect reward-based processing (McLean et al 2004) and tests involving reward/punishment processing are affected by dopamine depletion (Roiser et al 2005). A lack of D_2 receptors and/or dopamine depletion states have been implicated in a number of conditions or destructive behaviours thought to be caused by poorly functioning biochemical reward systems.

Individuals tend to be at risk of multiple addictive, impulsive and compulsive behavioural problems, such as severe alcoholism, cocaine, heroin, marijuana and nicotine addiction, pathological gambling, sex addiction, chronic violence, post-traumatic stress disorder, risk-taking behaviours and antisocial behaviour. As such, the use of tyrosine as a precursor to dopamine has a theoretical basis for use in this condition (Blum et al 2000).

Reward deficiency syndrome has also been proposed as a possible mechanism explaining the tendency to drug and alcohol addiction in schizophrenia (Green et al 1999).

To date, no large controlled studies are available to determine the clinical effects of tyrosine supplementation in this condition.

Drug withdrawal

Tyrosine has been used to aid in the withdrawal of cocaine, caffeine and nicotine. Anecdotal reports suggest it is successful; however, large controlled studies are not available to determine clinical significance.

L-tyrosine supplementation has been considered because chronic cocaine use is believed to cause catecholamine depletion and cocaine withdrawal has been associated with major depression. To date, results from trials using tyrosine as a stand-alone treatment during cocaine withdrawal have produced disappointing results (Chadwick et al 1990, Galloway et al 1996). Although untested as yet, the effects of tyrosine may be of most assistance where a deficiency of dopamine D_2 receptors is suspected, such as in reward deficiency syndrome.

Stress adaptation

Physical and emotional stress can impair performance and memory. In order to reduce the adverse effects of stress on these functions, improvements in stress adaptation are sought, including through the use of supplements such as tyrosine. Tyrosine appears to enhance the release of catecholamines when neurons are firing at an increased rate due to stress, but not at their basal rates (Young 2007). Several clinical studies have explored the effects of tyrosine in volunteers exposed to stressful situations, generally producing positive results on some parameters (see 'Clinical note: allostatic responses to stress' in the Siberian ginseng monograph for more information about stress adaptation). A number of studies have been conducted by the US and Dutch military, so extrapolation to other population groups should be made with caution.

Tyrosine supplementation was found to reduce the effects of stress and fatigue on cognitive performance in a study conducted with a group of 21 cadets during a demanding military combat training course. Subjects received a protein-rich drink containing (2 g) tyrosine five times daily or a carbohydrate-rich drink with the same amount of calories (255 kcal). Assessments on day 6 of the

course showed that the tyrosine group performed better on a memory and a tracking task than the control group and further experienced a decrease in systolic blood pressure; however, no effects on mood were observed (Deijen et al 1999).

Other studies indicate that high-dose tyrosine (150 mg/kg) may also improve some aspects of performance and help sustain working memory when multi-tasking in stressful situations. One placebo-controlled trial involving 20 people found that administration of tyrosine significantly enhanced accuracy and working memory during the multiple task battery 1 hour after ingestion. However, tyrosine did not significantly alter performance on the arithmetic, visual or auditory tasks during the multiple task, or modify any performance measures during the simple task battery (Thomas et al 1999).

Cold stress

Similar results were obtained in another controlled trial that investigated the effects of tyrosine (150 mg/kg) on memory tasks in cold (4°C) conditions. Two hours after ingesting L-tyrosine, matching accuracy significantly improved in the cold and was at the same level as administration of either tyrosine or placebo at a comfortable 22°C (Shurtleff et al 1994). Two small trials have shown that tyrosine supplementation (total 300 mg/kg) alleviates working memory decrements induced by cold exposure (~10°C) (Mahoney et al 2007) and may also improve the psychomotor task of marksmanship (O'Brien et al 2007).

Other beneficial effects have been obtained with tyrosine supplementation in volunteers exposed to cold stress. A double-blind, placebo-controlled, crossover study found that tyrosine (100 mg/kg) could protect humans from some of the adverse consequences of a 4.5 hour exposure to cold and hypoxia. Tyrosine significantly decreased symptoms, adverse moods and performance impairment in subjects who exhibited average or greater responses to these environmental conditions (Banderet & Lieberman 1989).

OTHER USES

Premenstrual syndrome

Although tyrosine is used to reduce symptoms of irritability, depression and fatigue associated with PMS, this is largely based on theoretical considerations and the observation that a significant reduction in tyrosine levels occurs during the premenstrual period according to one study (Menkes et al 1994).

This study further found that tryptophan depletion caused a significant aggravation of premenstrual symptoms, particularly irritability, and symptom magnitude was correlated with reduction in tryptophan relative to other amino acids.

Reproductive effects

Although no controlled studies are available, tyrosine is sometimes used for lowered libido as it indirectly increases testosterone and dopamine levels, both factors important in this condition. Five female lambs with delayed puberty who received a single oral dose of L-tyrosine (100 mg/kg bodyweight) exhibited significantly higher progesterone concentrations than a control group. Three came into heat and two became pregnant compared to none in the control group (El-Battawy 2006).

Parkinson's disease

Administration of tyrosine has been shown to increase dopamine production in the CNS of patients with Parkinson's disease (Growdon et al 1982).

Weight loss

Tyrosine is thought to potentially suppress appetite and stimulate brown adipose tissue due to its enhancement of noradrenaline synthesis. Additionally, as a precursor for thyroid hormones it may also increase the basal metabolic rate.

Chronic fatigue syndrome

Low tyrosine levels have been identified in subjects with chronic fatigue syndrome, suggesting a possible role for supplementation in this condition (Georgiades et al 2003).

Narcolepsy

Abnormalities of the dopaminergic system are thought to be part of the underlying aetiology of this disorder, therefore tyrosine is used on the theoretical basis that an increase in dopamine levels will produce an improvement (Roufs 1990).

A randomised, double-blind placebo-controlled study of L-tyrosine (9 g/day for 4 weeks) that tests this theory has been conducted in 10 subjects with narcolepsy and cataplexy. While receiving tyrosine, subjects reported feeling less tired, less drowsy and more alert; however, ratings of daytime drowsiness, cataplexy, sleep paralysis, night-time sleep, overall clinical response, and measurements of multiple sleep latency and tests of speed and attention did not detect a significant difference with placebo (Elwes et al 1989). An earlier trial of longer duration, however, reported that within 6 months all eight participants were free from daytime sleep attacks and cataplexy (Mouret et al 1988b).

Nemaline myopathy

Five patients (4 infants and 1 adolescent) with nemaline myopathy (facial and bulbar weakness resulting in chewing and swallowing difficulties, recurrent aspiration, and poor control of oral secretions) received L-tyrosine (250 to 3000 mg/day). All infants experienced an initial decrease in sialorrhoea and an increase in energy levels. The adolescent experienced improved strength and exercise tolerance (Ryan et al 2008).

DOSAGE RANGE

- As tyrosine is considered to be a non-essential amino acid there is no specific recommended daily intake. The typical dose in clinical trials appears to be 100–150 mg/kg. Divided dosing may be beneficial as levels remain above baseline for 6-8 hours following administration.
- Depression, PMS and chronic fatigue: 500–1000 mg before meals three times daily.

- Stress: 1500 mg/day in divided doses.
- Decreased libido, Parkinson's disease, drug detoxification, and weight loss: 1–2 g/day in divided doses.
- Natural stimulant: 500–1000 mg on an empty stomach first thing in the morning.
- Alertness following sleep deprivation: 150 mg/kg/day.
- As individual sensitivity to tyrosine can vary, it is recommended to start at 100 mg/day and gradually increase dose (Cass & Holford 2001).

ADVERSE REACTIONS

Migraine headache, mild gastric upset, nausea, headache, fatigue, heartburn, arthralgia, insomnia and nervousness (Hendler & Rorvik 2001).

High blood pressure may occur in susceptive individuals — hypertensive patients taking tyrosine should be monitored closely.

SIGNIFICANT INTERACTIONS

Amphetamine, ephedrine, phenylpropanolamine

L-Tyrosine (200 and 400 mg/kg) has been shown to increase the side-effect of anorexia caused by phenylpropanolamine, ephedrine and amphetamine in a dose-dependent manner in rats (Hull & Maher 1990) — observe patients using this combination.

Antidepressant drugs

Monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants or selective serotonin reuptake inhibitors (SSRIs): Theoretically, concurrent use may result in elevated blood pressure and/or enhanced antidepressant effects. In the case of MAOIs some tyrosine may be metabolised to tyramine and concurrent use with MAOIs may lead to a hypertensive crisis.

Tyrosine should be avoided unless under medical supervision.

CNS stimulants

Tyrosine is a precursor to a number of neurotransmitters so additive effects may occur — caution.

Levodopa

L-Dopa competes with tyrosine for uptake, therefore concurrent use may decrease uptake of both substances, reducing efficacy (Riederer 1980, DiPiro et al 1999, Awad 1984) — avoid unless under medical supervision.

Morphine sulfate

L-Tyrosine potentiates morphine-induced analgesia 154% in mice (Hull et al 1994). Observe patients taking tyrosine and morphine sulfate concurrently — potential beneficial interaction.

Thyroid hormone medication

Additive effects possible because tyrosine is a precursor to thyroid hormones — observe patients taking tyrosine concurrently with thyroid hormone medication.

CONTRAINDICATIONS AND PRECAUTIONS

- Malignant melanoma: a theoretical concern exists that tyrosine supplementation may promote the division of cancer cells (McArdle et al 2001). Tyrosine is contraindicated until safety is established.
- Manic conditions: due to the theoretical possibility that tyrosine may significantly increase neurotransmitter synthesis, close medical supervision is required (Cass & Holford 2001).
- Hyperthyroidism and Graves' disease: theoretically tyrosine may aggravate these conditions as it is a precursor to thyroxine (van Spronsen et al 2001).
- Alkaptonuria and tyrosinaemia (inborn errors of tyrosine metabolism).
- Hypertension: use tyrosine with caution at high dose.
- Ecstasy users should be aware that MDMA increases the concentration of tyrosine in the brain causing long-term depletion of 5-HT (Breier et al 2006).

PREGNANCY USE

High-dose supplements should be used with caution in pregnancy.

PATIENTS' FAQs

What will this supplement do for me?

Tyrosine supplementation appears to increase the levels of important brain chemicals and thyroid hormones. As such, it may elevate mood and alertness, and enhance the body's ability to deal with stress.

When will it start to work?

Although some research suggests that effects begin within 1–2 hours, it may take up to 1 week for maximal effects to be seen.

Are there any safety issues?

Theoretically, tyrosine may increase blood pressure in susceptible individuals and also interact with a number of medicines such as pharmaceutical antidepressants and thyroid treatment. It is also not recommended in pregnancy.

PRACTICE POINTS/PATIENT COUNSELLING

- Tyrosine is a conditionally essential amino acid that is ingested from the diet or produced from phenylalanine in the body.
- Many of the pharmacological actions of tyrosine relate to its role as a precursor to a number of neurotransmitters and thyroid hormones.
- Protein sources enriched with tyrosine but lacking in phenylalanine are used in PKU.
- Tyrosine supplements are used to improve cognitive function, in the management of depression or reward deficiency syndrome associated with noradrenaline or dopamine depletion, and to enhance stress adaptation systems.
- Due to its effects on neurotransmitters, it may elevate blood pressure in susceptible people when taken in high doses, and increase the effects of amphetamines, ephedrine, phenylpropanolamine, thyroxine and pharmaceutical antidepressants.

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Valerian

HISTORICAL NOTE The sedative effects of valerian have been recognised for over 2000 years, having been used by Hippocrates and Dioscorides in ancient Greece. Over the past 500 years, valerian was widely used in Europe as a calmative for nervousness or hysteria and also to treat dyspepsia and flatulence. Legend has it that the Pied Piper put valerian in his pockets to attract the rats out of Hannover. Valerian was widely used by the Eclectic physicians and listed in the United States Formulary until 1946.

COMMON NAME
Valerian

OTHER NAMES
All-heal, amantilla, balderbrackenwurzel, baldrian, baldrianwurzel, fragrant valerian, heliotrope, herbe aux chats, katzenwurzel, phu germanicum, phu parvum, valeriana, wild valerian

BOTANICAL NAME/FAMILY
Valeriana officinalis (family Valerianaceae)

PLANT PART USED
Rhizome

CHEMICAL COMPONENTS
Valtrates, didrovaltrates, isovaltrates, monoterpenes, sesquiterpenes, caffeic, gamma-amino butyric and chlorogenic acids, beta-sitosterol, methyl 2-pyrrolketone, choline, tannins, gum, alkaloids, a resin. Essential oils (0.5–2%) in the plant contain the compounds bornyl acetate and the sesquiterpene derivatives valerenic acid, valeranone and valerenal.

The chemical composition of valerian varies greatly depending on such factors as plant age and growing conditions. Processing and storage of the herb also affects its constituents, such as the iridoid esters, which are chemically unstable.

MAIN ACTIONS

Anxiolytic and hypnotic
Extensive pharmacological research has been conducted; however, identifying the main active constituents in valerian and their mode of action remains unclear and several neurobiological mechanisms are believed to be at work. In vitro tests so far have demonstrated that valerian stimulates the release of GABA, inhibits GABA reuptake and may have an effect at GABA receptors (Ortiz et al 1999, Santos et al 1994). There is also evidence of agonist effects at the human A_1 adenosine receptor for the methanolic extract (Schumacher et al 2002).

A recent study using a rat model identified anxiolytic and antidepressant activity for an ethanolic extract of valerian (phytofin Valerian 368) (Hattesohl et al 2008).

Both in vivo and numerous clinical studies confirm sedative or hypnotic activity (Ammer & Melnizky 1999, Balderer & Borbely 1985, Della Loggia et al 1981, Donath et al 2000, Dorn 2000, Leathwood & Chauffard 1985, Gerhard et al 1996, Gessner & Klasser 1984, Leuschner et al 1993, Lindahl & Lindwall 1989, Schulz et al 1994, Wheatley 2001).

Antispasmodic
Both in vitro and in vivo studies provide evidence of antispasmodic activity on smooth muscle (Hazelhoff et al 1982).

OTHER ACTIONS
A pharmacokinetic study with healthy adults found that typical doses of valerian are unlikely to produce clinically significant effects on the CYP2D6 or CYP3A4 pathways of metabolism (Donovan et al 2004). These results were confirmed in another human pharmacokinetic study that found no evidence that valerian affects CYP3A4/5, CYP1A2, CYP2E1 and CYP2D6 activity (Gurley et al 2005).

CLINICAL USE
In practice, valerian is rarely used as a stand-alone treatment and is often combined with other sedative or relaxant herbs, such as chamomile, passionflower, skullcap, lemon balm and hops.

Insomnia
Numerous RCTs have investigated the effects of different valerian preparations as a treatment for insomnia. Some studies have involved people with confirmed sleep disturbances and others involved healthy subjects with no sleep problems. Treatment time-frames varied from acute (1 dose) to longer term (over 1 month) and doses have varied considerably. Some studies use only subjective data such as self-reported sleep quality whereas others use objective measures such as polysomnographs. As a result, interpreting the evidence is difficult and no clear picture strongly emerges. Overall, it appears that some preparations have benefits for poor sleepers and valerian may be better suited to reducing sleep latency rather than other disturbances, but this is not yet a definitive conclusion. Findings from a pharmacokinetic study however lend support to this conclusion, as it demonstrated that valerenic acid (a pharmacologically active marker compound for valerian) was increased in serum within an hour after ingestion, reached maximal levels between 1 and 2 hours then fell, with no detectable levels observed after 4 hours (Anderson et al 2005). This pharmacokinetic pattern is also consistent with the finding that valerian does not produce residual morning sedation.

A number of different valerian products have been studied in clinical trials (e.g. Baldosedron, Baldrien-Dispert, Euvegal, Harmonicum Much, Seda-Kneipp, Sedonium, Valdispert, Valverde and Valerina Nutt). The LI 156 valerian extract is one of the most studied.

A systematic review by Stevinson and Ernst (2000) identified 19 studies involving valerian treatment that were published prior to May 1999. Of these, nine were chosen for inclusion because they were randomised, measured sleep parameters and tested single ingredient valerian products. Three studies considered the cumulative effects of long-term use of valerian whereas six investigated the effects of single-dose treatment. Two of the three studies investigating repeated administration of valerian found that effects were established by 2 weeks. The most rigorous placebo-controlled study showed that valerian LI 156 (600 mg) produced improvement on nearly all measures between weeks 2 and 4 (Vorbach et al 1996 as reported by Stevinson & Ernst 2000). The 4-week study involved 121 volunteers and assessed clinical effectiveness using four validated rating scales. At the end of the study, valerian was rated better than placebo on the Clinical Global Impression Scale, and at study conclusion (day 28) 66% of patients rated

valerian effective, compared to 26% with placebo. Of the six studies investigating acute effects, valerian produced positive results in three whereas in the other three it was no better than placebo.

Interpretation of study results is difficult because of varying research methodologies. For example, some studies used surveys whereas others used EEG readings, some were conducted at home and others in hospitals or sleep laboratories, and pre-bedtime variables (e.g. caffeine consumption) were not fully controlled. Additionally, some studies used healthy volunteers with no sleep disturbances with little scope to observe further improvements. Since then, several other studies have been published.

In 2007, a comprehensive systematic review conducted by Taibi et al identified 37 separate studies of which 29 were controlled trials which evaluated valerian for both efficacy and safety, and eight were open-label trials which evaluated for safety only (Taibi et al 2007). The search was not limited to English language publications, thereby identifying many additional studies published by European research groups, including 17 studies published in German. The review evaluated data from RCTs and trials of other designs which investigated ethanolic extracts of valerian, aqueous extracts of valerian and valerian herbal combination treatments in people with sleep disturbances and in those who were considered healthy.

Six randomised, double-blind studies of an ethanolic extract of valerian (mainly LI 156 Sedonium®) at a dosage between 300 and 600 mg before bedtime were assessed (Taibi et al 2007). Two studies measured polysomnographic outcomes and 4 collected only subjective measures of sleep quality. Overall, the ethanolic extract was not found to significantly affect objective or subjective sleep outcomes compared to placebo, however it did improve subjective sleep quality ratings in a manner similar to benzodiazepines. If we assume benzodiazepines perform better than placebo, then this is a positive outcome.

Seven studies evaluated the effects of aqueous preparations of valerian (Valdispert® Dixa SA Switzerland) at doses ranging from 400 mg/night to 450 mg three times daily (Taibi et al 2007). Four studies involved healthy subjects, 2 were of elderly people with sleep disturbances and one study was of people with difficulties in sleep onset. Once again, methodologies were highly varied. Only one study excluded volunteers with medical conditions that could contribute to poor sleep. As may be expected with such variations, results were mixed. The two studies involving elderly volunteers produced contradictory results whereas reduced subjective latency was demonstrated in people with sleep onset disturbances. Healthy volunteers appeared to gain no benefit from the treatment.

Five further studies used valerian extracts which were standardised to valepotriate content (Taibi et al 2007). Three of these studies used *V. edulis* (one used Harmonicum Much®) as a source of valepotriates and one used *V. wallichii* (Valmane®). The dose of valepotriates varied from 60 to 120 mg and one preparation of *V. officinalis* used a preparation standardised to 450 mg of valerenic acid (Mediherb, QLD Australia). Whilst methodologies varied considerably, overall standardised extracts appeared to reduce sleep disturbances when compared to placebo. A dose of 100 mg valepotriates taken three times a day was found to significantly improve sleep quality ratings in people withdrawing from benzodiazepines when compared to placebo. Additionally, 60 to 120 mg valepotriates was similarly effective in people who had reported disturbed sleep.

Valerian herbal combinations featured in 10 studies overall, valerian–lemon balm in 4 and valerian–hops in 6 (Taibi et al 2007). The studies using valerian–lemon balm combinations were shown to reduce sleep latency and increase sleep quality in people suffering sleep disturbances whereas no change was observed in healthy subjects. In contrast, studies with valerian–hops combinations found no significant improvements using polysomnographic equipment or subjective sleep outcomes (Taibi et al 2007). The hops–valerian treatments used were ZE 91019 (Alluna®) or another product Hova® (extraction unknown).

In 2007, a later randomised placebo controlled study was published which compared a valerian–hops combination (Ze 91019) to valerian monotherapy (Ze 911) (Koetter et al 2007). The herbal combination treatment contained the same amount of valerian (500 mg) as monotherapy, thereby allowing researchers to evaluate what contribution hops (120 mg) would make to the outcomes measured. Volunteers suffering from non-organic insomnia were given either treatment or placebo for 4 weeks. In contrast to previous studies cited by Taibi et al, the valerian–hops combination was significantly superior to placebo in reducing sleep latency, improving clinical global impression scores and increasing slow-wave sleep, whilst the single valerian extract failed to show benefits beyond placebo.

Comparisons with benzodiazepines

Three randomised studies have compared valerian monotherapy with benzodiazepine drugs. One double-blind trial found that subjects treated with either 600 mg valerian (ethanolic extract) or 10 mg oxazepam experienced significantly improved sleep, with no statistically significant differences detected between the treatments (Dorn 2000). Another study comparing the immediate sedative effects and residual effects of a valerian and hops preparation, a sole valerian preparation, flunitrazepam and placebo found that subjective perceptions of sleep quality were improved in all treatment groups; however, only flunitrazepam treatment impaired performance the morning after, as assessed both objectively and subjectively (Gerhard et al 1996). Furthermore, 50% of subjects receiving flunitrazepam reported mild side-effects compared with only 10% from the other groups.

A 2002 double-blind randomised trial compared the effects of valerian extract LI 156 (Sedonium) 600 mg/day to 10 mg oxazepam over 6 weeks in 202 patients with non-organic insomnia (Ziegler et al 2002). The multicentre trial took place at 24 study centres in Germany and found that valerian

treatment was at least as efficacious as oxazepam, with both treatments improving sleep quality. Subjectively, 83% of patients receiving valerian rated it as 'very good' compared with 73% receiving oxazepam.

Children

The efficacy and tolerability of a valerian and lemon balm combination (Euvegal® forte) was tested in a large, open, multicentre study of 918 children (aged under 12 years) with restlessness and nervous sleep disturbance (dyssomnia) (Muller & Klement 2006). Both investigators' and parents' ratings revealed a reduction in the severity of symptoms for most patients. The study reported that 81% of children with dyssomnia experienced an improvement and 70% of children with restlessness improved. Treatment was generally rated as good or very good and considered well tolerated. Each Euvegal® forte tablet consisted of 160 mg valerian root dry extract (*Valeriana officinalis* L.) with a drug-extract ratio of 4–5:1 (extraction solvent ethanol 62% v/v) and 80 mg lemon balm leaf dry extract (*Melissa officinalis*) with a drug-extract ratio of 4–6:1 (extraction solvent ethanol 30% v/v). The standard dosage of Euvegal® forte (4 tablets daily) was used by 75% of patients and chosen by the investigator.

Anxiety and psychological stress states

Less investigation has taken place to determine the role of valerian as a treatment for anxiety states.

A randomised study found that low-dose valerian (100 mg) reduced situational anxiety without causing sedation (Kohnen & Oswald 1988). Positive results were also obtained in a smaller open study of 24 patients suffering from stress-induced insomnia who found treatment (valerian 600 mg/day for 6 weeks) significantly reduced symptoms of stress and insomnia (Wheatley 2001). Another randomised trial compared the effects of a preparation of valepotriates (mean daily dose 81.3 mg) with diazepam (mean daily dose 6.5 mg) and placebo in 36 outpatients with GAD under double-blind conditions (Andreatini et al 2002). After 4 weeks' treatment, all groups had significant reductions in Hamilton anxiety (HAM-A) scale scores; however, only those receiving valepotriates or diazepam showed a significant reduction in the psychic factor of HAM-A.

Kava kava is a herbal medicine also used in the treatment of anxiety and found to be effective in clinical studies (Pittler & Ernst 2002). A study that compared the effects of kava kava to valerian and placebo in a standardised mental stress test found that both herbal treatments reduced systolic blood pressure, prevented a stress-induced rise in heart rate and decreased self-reported feelings of stress (Cropley et al 2002).

A 2006 Cochrane review concluded there is insufficient evidence to draw any conclusions about the efficacy or safety of valerian compared with placebo or diazepam for anxiety disorders (Miyasaka et al 2006). RCTs involving larger samples and comparing valerian with placebo or other interventions used to treat of anxiety disorders, such as antidepressants, are needed.

Muscle spasm and cramping

Valerian preparations have long been used to treat a wide variety of gastrointestinal disorders associated with spasms such as diarrhoea, colic and irritable bowel. It has also been used to relieve cramping in dysmenorrhoea. Although no controlled studies are available to confirm clinical effectiveness in these conditions, valerian is likely to exert some degree of antispasmodic activity based on its pharmacological actions.

OTHER USES

Fibromyalgia

One randomised study, which was investigator blinded, tested the effects of whirl baths with plain water or with water containing pine oil or valerian on pain, disturbed sleep and tender point count in 30 outpatients with generalised fibromyalgia. Valerian significantly improved wellbeing and sleep together with decreasing tender point count, whereas baths with pine oil worsened pain and plain water baths reduced pain but had no effect on wellbeing and sleeplessness (Ammer & Melnizky 1999).

Benzodiazepine withdrawal

Although no clinical studies are available, the herb is also used in practice to reduce dependency on benzodiazepine drugs. Valerian is prescribed together with other herbal medicines and psychological counselling while the benzodiazepine dose is slowly reduced.

DOSAGE RANGE

- Infusion of dried root: 3–9 g/day.
- Liquid extract (1:2): 2–6 mL/day.
- Tincture (1:5): 5–15 mL/day.
- When used for insomnia, valerian should be taken approximately 1 hour prior to bedtime.

According to clinical studies

- Anxiety: 100 mg–600 mg/day of the dried root or valepotriates (mean daily dose 81.3 mg).
- Insomnia: doses above 600 mg/day of dried root taken 1 hour before bedtime. Ethanolic extract of valerian: 300–600 mg before bedtime. Aqueous preparations of valerian: 400 mg/night to 450 mg three times daily. Standardised extracts: 60–120 mg valepotriates or 450 mg of valerenic acid before bedtime.
- For benzodiazepine withdrawal: 100 mg valepotriates taken three times daily

TOXICITY

According to one case report, a dose of valerian taken at approximately 20-fold the recommended therapeutic dose appears to be benign (Willey et al 1995).

ADVERSE REACTIONS

As with numerous pharmaceutical sedatives, next morning somnolence is a possible side-effect of therapy; however, evidence from two human studies suggests this is not associated with valerian use (Gerhard et al 1996, Kuhlmann et al 1999).

Additionally, evidence from a pharmacokinetic study indicates this is highly unlikely.

Vivid dreams were reported in one study; however, this is considered rare by clinicians (Wheatley 2001).

Paradoxical effects have been observed in clinical practice; however, this also appears to be rare (Mills & Bone 2000).

Occasionally, headache and gastrointestinal symptoms have been reported (Ernst 2001).

SIGNIFICANT INTERACTIONS

Pharmaceutical sedatives

Theoretically, potentiation effects may occur at high doses; however, this has not been tested under clinical conditions — observe patients taking valerian concurrently with pharmaceutical sedatives.

Alcohol

RCTs have shown no potentiation effects with alcohol use (Ernst 2001).

CONTRAINDICATIONS AND PRECAUTIONS

No known contraindications. Care should be taken when driving a car or operating heavy machinery when high doses are used.

PREGNANCY USE

No restrictions are known; however, safety has not been well established in pregnancy. No significant negative effects have been reported in toxicological tests with animals and none reported in clinical studies (Upton 1999).

PATIENTS' FAQs

What will this herb do for me?

Valerian is classified as a mild, sedative herbal medicine. It can reduce the time it takes to fall asleep at night and may also relieve stress and anxiety during the day. When added to a bath, it may increase relaxation, wellbeing and reduce some forms of pain.

When will it start to work?

For some, it works within an hour of the first dose; however, research suggests it works best after several weeks of regular use.

Are there any safety issues?

From the available evidence, next-day drowsiness is uncommon and physical addiction highly unlikely. Taking high doses during the day may increase drowsiness, so care is needed when driving a car or operating heavy machinery.

PRACTICE POINTS/PATIENT COUNSELLING

- There is good scientific evidence to support the use of valerian as a treatment for insomnia; however, it appears that ongoing use may be more effective than single-dose use and effects on sleep progress over several weeks.
- It appears to be best suited to reducing sleep latency (i.e. time taken until falling asleep) and improves subjective assessments of sleep.
- There is no evidence of next-day somnolence or significant adverse effects.
- Valerian also relieves symptoms of stress and anxiety, with several studies observing effects similar to benzodiazepines; however, further research is required.
- Due to its pungent odour, solid-dose forms may be preferable.

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Vitamin A

HISTORICAL NOTE In ancient Egypt and Greece, physicians recommended the liver of an ox to cure night blindness. Although this could be interpreted as applying the liver locally, it could also refer to ingesting some, which would have provided a good source of vitamin A and proven to be a cure for night blindness caused by deficiency (Shils et al 2006). Modern day scientific research into vitamin A began in 1913, with its discovery at both Yale and Wisconsin Universities. Researchers at both sites independently noticed that the substance could promote survival and growth of young animals. Since then, each decade has brought important new discoveries about vitamin A. The period from the 1960s to 1980s was particularly fruitful, as several proteins essential for transport and metabolism of vitamin A were isolated and purified. During the 1980s, another major discovery was made when a link between childhood mortality and subclinical deficiency was identified. Vitamin A research continues to interest a wide spectrum of researchers and influence public health initiatives.

BACKGROUND AND RELEVANT PHARMACOKINETICS

The term 'vitamin A' refers to a family of fat-soluble dietary compounds that are structurally related to retinol, and share its biological function. Vitamin A is found in foods as itself or as a precursor, which is converted into vitamin A in the body. The precursors, known as carotenes, are found in deep yellow, green and red coloured plants.

Retinyl esters, retinol or carotenoids from the diet, or supplements, are hydrolysed in the small intestine where they are absorbed as retinol into the mucosal cells (Miller et al 1998). Entering the body within the lipid core of chylomicrons, they are transported through lymph to blood, where it then recycles between plasma and tissues numerous times, before arriving at the liver. The liver performs three key tasks in relation to vitamin A. It is responsible for regulating the secretion of retinol to specific transport proteins known as 'retinol-binding proteins', it serves as a major storage organ and is the major site of vitamin A catabolism. Vitamin A metabolites are excreted mainly through the faeces and urine.

The body has a good capacity for vitamin A storage; however, its ability to rapidly dispose of excess vitamin A is quite limited (Shils et al 2006). This may explain why vitamin A can accumulate to toxic levels when intake greatly exceeds requirements.

This monograph will focus on preformed vitamin A and retinoic acid only. Further information about the carotenoids can be found in other monographs.

FOOD SOURCES

Preformed vitamin A (retinyl esters) is chiefly found in foods of animal origin, such as liver, red meat and eggs, as well as in fish, milk, butter and cream.

Cooking can destroy up to 40% of the vitamin A content of food (Wahlqvist et al 1997).

DEFICIENCY SIGNS AND SYMPTOMS

- Night blindness, which can progress to complete blindness if left untreated.
- Keratinisation of epithelial surfaces, causing them to dry and harden.
- Poor dental health.
- Compromised immune function.
- Reduced reproductive capabilities.

Primary deficiency

Primary deficiency is caused by prolonged dietary deprivation. In large areas of the world, vitamin A deficiency is endemic, causing widespread blindness and mortality (Sklan 1987).

Secondary deficiency

Secondary deficiency can develop when absorption, storage or transport is reduced or carotene is not adequately converted to vitamin A. Conditions associated with risk of secondary deficiency

include malabsorption syndromes, such as coeliac disease and cystic fibrosis (CF), pancreatic disease, duodenal bypass, congenital partial obstruction of the jejunum, obstruction of the bile ducts, giardiasis, diabetes and kwashiorkor.

MAIN ACTIONS

Vitamin A is an essential nutrient required for life and serves two very different biological functions. First, in the form of retinaldehyde, it constitutes the light-sensitive component of the retina, rhodopsin, and second, in the form of retinoic acid, it activates a large number of transcription factors (McCaffery & Drager 1993).

Antioxidant

Vitamin A exhibits free radical scavenging properties.

Growth and development

Vitamin A is essential for embryonic growth. Deficiency, as well as excess, has been shown to be teratogenic in animal studies, suggesting the same may be true in humans. It is currently unclear whether vitamin A itself or one of its metabolites or both are responsible for the teratogenic effects seen with high exposure (Miller et al 1998).

Vitamin A is also necessary for healthy bone formation in children.

Immune function and maintenance of epithelial surfaces

Vitamin A maintains the health of epithelial cells in the body, which form an important barrier to infection, and the function of the immune system. More specifically, studies in animal models and cell lines show that vitamin A and related retinoids play a major role in immunity, including expression of mucins and keratins, lymphopoiesis, production of antibodies, and the function of neutrophils, natural killer (NK) cells, macrophages, T-lymphocytes and B-lymphocytes (Semba 1999). It has also been shown to potentiate antibody responses and lymphocyte proliferation in response to antigens and restore the integrity and function of mucosal surfaces (Semba 1994).

Vision

Vitamin A is involved in ocular health and function in two distinct ways. First, in the form retinaldehyde, it is an essential component of rhodopsin and is necessary for maintaining vision (Wahlqvist et al 1997). Deficiency states initially cause a reversible night blindness that can progress to complete blindness due to photoreceptor degeneration (McCaffery & Drager 1993). Second, as retinoic acid, it maintains normal differentiation of cells in the conjunctiva, cornea and other ocular structures, with deficiency resulting in xerophthalmia (dry eye) and corneal ulceration. In xerophthalmia, the cells lining the cornea lose their ability to produce mucus, and therefore lubrication of the eye becomes compromised. Dirt particles that eventually enter the eye are more easily able to scratch the surface, increasing the risk of infection and, ultimately, blindness.

Chemoprevention

Studies in cell culture and animal models have documented the capacity for natural and synthetic retinoids to reduce carcinogenesis significantly in skin, breast, liver, colon, cervical, prostate and other sites (Ross 1999). The mechanism of action responsible has not been fully elucidated, but several theories exist. It has been known since early in the 20th century that vitamin A deficiency can induce metaplastic changes to epithelial cells (De Luca et al 1997). Retinoic acid is thought to act as an inhibitor of carcinogenesis by interfering with promotion rather than with initiation, which may be blocked by inhibition of proliferation, stimulation of differentiation or induction of apoptosis (Niles 2000). Other research suggests it may also inhibit the final stage when malignant conversion of a benign tumour to a carcinoma occurs (De Luca et al 1997).

CLINICAL USE

Deficiency: prevention and treatment

Traditionally, vitamin A supplementation has been used to treat deficiency or prevent deficiency in conditions associated with risk of vitamin A deficiency, such as diabetes, hyperthyroidism, protein deficiency, intestinal infections and infestations and CF.

Paediatrics

Reducing infection severity

Vitamin A deficiency impairs systemic immunity and increases the incidence and severity of infections during childhood, particularly measles and infectious diarrhoea. There is also evidence that infectious diseases, such as measles, will in turn depress serum retinol concentrations, by >30%, according to one study (Enwonwu & Phillips 2004). This phenomenon does not just occur in undernourished populations. A study of well-nourished children in the USA with measles identified that 50% had concurrent vitamin A deficiency (Arrieta et al 1992).

It is suspected that infectious diseases influence retinol metabolism through mechanisms that are more complex than simple loss of retinol stores (Enwonwu & Phillips 2004). Impaired synthesis of retinol-binding protein and transthyretin and decreased expression of the receptors for retinoic acid could also be responsible. As such, the use of vitamin A in the treatment of infectious disease is not limited to developing countries, but may also have application in well-nourished populations.

In areas where vitamin A deficiency may be present, the World Health Organization (WHO) recommends administration of an oral dose of 200,000 IU (or 100,000 IU in infants) of vitamin A per day for 2 days to children with measles (D'Souza & D'Souza 2002a, 2002b). It has also been recommended that prophylactic vitamin A supplements be given to all infants and young children (0–59 months), pregnant women and post-partum women, 6 weeks after delivery, in these same areas (Ross 2002).

According to a 2005 Cochrane review, the WHO recommendation of two large doses of

vitamin A does successfully lower the risk of death from measles in hospitalised children under the age of 2 years, but not in all children with measles (Huiming et al 2005).

Reducing secondary infections associated with measles

A meta-analysis of six clinical trials found a 47% reduction in the incidence of croup in children with measles who were treated with 200,000 IU of vitamin A on 2 consecutive days. One study in the analysis reported a 74% reduction in the incidence of otitis media, but this was not confirmed in others. A statistically significant decrease in the duration of diarrhoea, pneumonia, hospital stay and fever was also observed (D'Souza & D'Souza 2002a).

Reducing childhood mortality

It has been estimated that a 23% reduction in young child mortality is possible with improvements in vitamin A status. This is most marked for deaths due to acute gastroenteritis and measles, but not acute respiratory infections or malaria (Ramakrishnan & Martorell 1998) and is particularly the case for older preschool children, whereas the effect on infants is less clear. In areas of endemic vitamin A deficiency, vitamin A supplementation was not found to lower the incidence of illness such as diarrhoea, dysentery or fever; however, it did reduce mortality with fewer case fatalities in young children with these diseases compared to placebo (Tielsch et al 2007). In newborn infants supplemented with 50,000 IU of vitamin A, all-cause mortality at 6 months was reduced by 15% (Klemm et al 2008).

Reducing febrile neutropenia

In a cohort of 49 children with cancer, those with plasma retinol levels below20 microgram/dL at diagnosis had a greater risk of developing episodes of febrile neutropenia compared to children with higher vitamin A status (Wessels et al 2008).

Very low birth weight (VLBW) infants

Supplementing VLBW infants with intramuscularly administered vitamin A is associated with a reduction in death or oxygen requirement at 1 month of age (Darlow & Graham 2007).

Reducing the risk of HIV transmission from mother to infant

The dominant mode of acquisition of HIV infection for children is mother-to-child transmission. Currently, this results in more than 2000 new paediatric HIV infections each day worldwide. A 2005 Cochrane review analysed results from four trials, which enrolled 3033 HIV-infected pregnant women, and found no evidence to support the use of vitamin A supplementation for this indication (Wiysonge et al 2005). One benefit that was identified for vitamin A supplementation was an improvement in infant birth weight. Neither maternal nor neonatal vitamin A supplementation significantly affected the overall mortality of children exposed to HIV by 2 years of age. Interestingly in infants who were HIV-negative at baseline but positive by 6 weeks of age, supplementation reduced mortality by 28%, whereas in infants who did not become HIV-positive by 6 weeks, supplementation doubled the risk of mortality by age 2 years. It has been suggested that vitamin A supplementation may have increased viral load among babies who subsequently became infected during breastfeeding, but this remains untested (Humphrey et al 2006b).

Fetal growth

Low levels of vitamin A impair fetal growth. In a cross-sectional study on 100 neonate–mother pairs, lower placental and neonatal levels of vitamin A were associated with prematurity and intrauterine growth retardation (Agarwal et al 2008).

Cancer prevention

Most forms of cancer arise from cells that are influenced by vitamin A (Wardlaw et al 1997). Combined with its antioxidant and immunomodulatory activities, vitamin A has been considered as a potential chemopreventive agent. Research thus far using cell cultures and animal models has identified the ability for natural and synthetic retinoids to reduce carcinogenesis significantly in skin, breast, liver, colon, prostate and other sites (Krinsky 2002). A look at the literature shows that impressive treatment results have mainly been obtained for synthetic retinoids and the relationship between natural vitamin A ingestion and cancer is less clear in humans.

In a cohort study of 3254 Japanese subjects aged from 39 to 85 years, high-serum levels of carotenoids were associated with reduced mortality rates of cancer of all sites or of cardiovascular disease, while high-serum levels of beta-carotene, total carotene, provitamin A and total carotenoids reduced risk of colorectal cancer or stroke at follow-up after 11.7 years. Serum retinol and tocopherols, however, were not associated with a reduction in risk of mortality from cancer or cardiovascular disease (Ito et al 2006).

Prostate cancer

A cohort study of 1985 men previously exposed to asbestos found whilst increasing intakes of vitamin C-rich vegetables such as peppers and broccoli were associated with reduced risk of prostate cancer, vitamin A intake (supplement of 7.5 mg retinol daily) did not lower risk (Ambrosini et al 2008). Similarly, in a large prospective study within the European Prospective Investigation into Cancer and Nutrition (EPIC) study, no associations were found between the plasma concentrations of carotenoids, retinol or tocopherols and overall prostate cancer risk (Key et al 2007).

Gastric cancer

In a large nested case–control study of patients with gastric cancer, a higher plasma concentration of beta-cryptoxanthin, zeaxanthin, retinol and alpha-tocopherol was associated with a significantly lower risk of developing gastric cancer (Jenab et al 2006). A high intake of vitamin A, alpha-carotene and beta-carotene was associated with a reduced

risk of gastric cancer in a prospective cohort study of 82,002 Swedish adults. However, no protective effect was found from beta-cryptoxanthin, lutein and zeaxanthin or lycopene intake (Larsson et al 2007). In contrast, a study among 36,745 Japanese subjects (aged 40–69) with *Helicobacter pylori* infection did not find a statistically significant association between plasma levels of retinol or lutein/zeaxanthin, lycopene, alpha- or gamma-tocopherol and the risk of gastric cancer (Persson et al 2008).

Lung cancer

A number of epidemiological studies have identified an inverse association between risk of lung cancer and serum carotenoid levels, but intervention studies have produced conflicting results. In general, vitamin A is supplied together with carotenoids making it difficult to determine the role of vitamin A as a stand-alone agent. (See Beta-carotene monograph for further discussion.) The pooled analysis of the primary data from eight prospective studies involving 430,281 subjects found those with the highest quintile of intake of vitamins A, C and E and folate from food-only had a statistically significant 28% reduction in the risk of lung cancer compared to those in the lowest quintile. This protective effect was lost, however, after adjusting for multiple risk factors for lung cancer, including smoking habits (Cho et al 2006). In a case-controlled study involving 333 patients diagnosed with primary lung cancer, however, a significantly lower risk of lung cancer was associated with a higher intake of vitamin A, alpha-carotene and beta-carotene rich food. Interestingly, no protective effect was observed for vitamin A consumed as supplements (Jin et al 2007). In patients exposed to blue asbestos, low plasma retinol levels were associated with increased risk of developing mesothelioma and lung cancer (Alfonso et al 2006). Patients with lung cancer have been found to have similar levels of retinol but lower levels of serum metabolites retinyl palmitate and retinoic acid levels compared to healthy controls, suggesting retinol metabolism may be impaired in these patients (Moulas et al 2006).

Other cancers

In a prospective cohort study involving 89,835 women aged between 40 and 59 years, dietary intake of carotenoids or vitamins A, C or E was not found to be associated with a reduced risk of ovarian cancer (Silvera et al 2006). While a prospective study of 88,759 women and 47,828 men found the intake of vitamins A and C from food was inversely associated with the risk of renal cell cancer in men, the total retinol intake from sources such as supplements, liver, vitamin A–fortified milk and cereals was not associated with a reduction in risk. The beneficial effects may possibly be due to other protective nutrients or chemicals in carotenoid-containing foods (Lee et al 2006).

Adjunct in chemotherapy

Vitamin A (350,000–500,000 IU/day) was randomly allocated to patients in a group of 100 with metastatic breast carcinoma treated by chemotherapy (Israel et al 1985). Patients supplemented with vitamin A showed a greater than two-fold increase in the complete response compared to controls (38% versus 15%; $P < 0.02$). Among chemotherapy responders in both groups, the projected 43-month survival rate was 93% in vitamin A-supplemented responders versus 30% in non-supplemented responders ($P < 0.02$).

Infections

Urinary tract

A placebo-controlled, double-blinded study involving 24 patients found a single dose of 200,000 IU vitamin A in addition to antimicrobial therapy significantly reduced recurrent urinary tract infections. In the treatment group, the rate of infection reduced to 0.12 attacks/month in the first 6-month period, and 0.29 attacks/month in the second 6-month period, compared to 0.47 attacks/month and 0.44 attacks/month respectively in the control group (Yilmaz et al 2007).

Lower respiratory tract

A recent Cochrane systematic review of nine randomised controlled trials (RCTs) involving 33,179 children examined the effectiveness and safety of vitamin A in preventing acute lower respiratory tract infections (LRTIs) in children up to 7 years old. Six studies used mega-dose vitamin A (100,000–206,000 IU) (every 4 months for a year or as once off), whilst four studies used low-dose (5000 IU daily, 10,000 IU weekly, 8333 IU weekly, and 20,000 IU or 45,000 IU every 2 months). Most studies did not find a beneficial effect on LRTI. Whilst two studies found vitamin A supplementation prevented acute LRTIs in children with low serum retinol or those with a poor nutritional status, unexpectedly three studies found vitamin A was associated with negative outcomes including an increased incidence of acute LRTI, and increased symptoms of cough, fever and rapid breathing. The authors concluded that the effect of vitamin A was influenced by the child's nutritional status or weight, with supplementation increasing the acute LRTI episodes in 'normal' children (Chen et al 2008).

HIV

The Zimbabwe Vitamin A for Mothers and Babies (ZVITAMBO) project examined the effects of a vitamin A supplementation on serum retinol concentration, and mortality and morbidity among HIV-positive and HIV-negative post-partum women. A single 400,000 IU dose of vitamin A given during the immediate post-partum period had no effect on maternal mortality of both HIV-negative and positive women after 2 years compared to placebo. Among HIV-positive women, the supplementation reduced clinic visits for treatment for malaria, cracked and bleeding nipples, pelvic inflammatory disease and vaginal infection, but did not lower overall rates of hospitalisation. Whilst vitamin A deficiency was more common among HIV-positive women, serum levels of retinol were unresponsive to supplementation except

in those with a CD4 count of less than 200 cells × 10^6/L (Zvandasara et al 2006). In a subsample of HIV-negative women enrolled in ZVITAMBO trial, a single dose of 400,000 IU vitamin A within 96-h post-partum did not reduce the incidence of HIV infection; however, HIV-negative women with low vitamin A levels (serum retinol < 0.7 micromol/L) were 10.4 times more likely to acquire HIV. In women with a low vitamin A who received supplementation, there was a slightly (non-significantly) lower incidence of HIV (Humphrey et al 2006a).

Dermatology

Numerous clinical studies have shown beneficial effects of vitamin A or its derivatives on skin diseases such as acne, psoriasis, ichthyoses, keratodermas, skin cancers, lichen planus and UV-induced skin damage and photo-ageing (Futoryan & Gilchrest 1994). Currently, most research has been conducted with synthetic retinoid derivatives and is not representative of the effects of natural vitamin A. In a study of 100 newly diagnosed, untreated acne patients (mean age 21 years), plasma levels of both vitamin A and vitamin E were found to be significantly lower compared to age-matched healthy controls. An inverse relationship was also found between plasma vitamin A concentrations and the severity of the acne (El-Akawi et al 2006).

Topical vitamin A improves the appearance of older skin, and may also increase its resistance to injury and ability to heal. A lotion containing 0.4% retinol was tested in a 6-month randomised controlled trial involving 36 elderly subjects aged between 80 and 96. The lotion was applied three times a week to left or right upper arm, with a lotion without retinol used on the other arm. The retinol-treated skin had fewer fine wrinkles and reduced roughness compared to the skin treated with the non-retinol lotion. The effects are due to an increase in glycosaminoglycan which helps the skin retain water, and increased collagen production (Kafi et al 2007).

Ophthalmological diseases

Retinitis pigmentosa

One randomised, double-blind trial found that people receiving 15,000 IU/day of vitamin A experienced a slowed rate of retinal function decline (Berson et al 1993). The mechanism responsible is poorly understood, but it is possible that vitamin A transport or the retention capacity of the retina is abnormal in retinitis pigmentosa; or, defects in the pigment epithelium involving vitamin-associated proteins occurs (Sharma & Ehinger 1999).

> ***Clinical note — Retinitis pigmentosa***
> Retinitis pigmentosa describes a group of hereditary retinal dystrophies, characterised by the early onset of night blindness followed by a progressive loss of the visual field. The underlying pathology is a defect that alters the function of the rod photoreceptor cell and subsequent degeneration of these cells (van Soest et al 1999).

Xerophthalmia

Xerophthalmia is responsible for at least half of all cases of measles-associated blindness and is the cause of at least half a million cases of paediatric blindness worldwide (Sommer 1998). This condition is associated with vitamin A deficiency and protein malnutrition.

Reducing morbidity and mortality of pregnant women

Vitamin A supplements have been recommended in pregnancy to improve outcomes, including maternal mortality and morbidity. There is a Cochrane review of five trials involving 23,426 women that investigated the effects of vitamin A supplementation during pregnancy, alone or in combination with other supplements (Van et al 2002). Trials were heterogeneous and difficult to pool; however, two trials from Nepal and Indonesia suggested beneficial effects of vitamin A supplementation. In addition, daily or weekly vitamin A supplementation reduced night blindness in pregnant women living in high-risk areas. Vitamin A during or after pregnancy has not been found to reduce post-partum mortality in HIV-positive women. See discussion under *Infections*.

Leucoplakia

A Cochrane review of treatments for the prevention of malignant transformation of leucoplakia identified five RCTs involving 245 patients which tested vitamin A and retinoids (used topically or as oral treatment), and one study each for beta-carotene and lycopene. Whilst these studies failed to demonstrate prevention of malignant transformation of leucoplakia, they were associated with a small but significant rate of clinical resolution when compared with placebo or absence of treatment. Retinoic acid and lycopene may also result in histological improvement, though results were based on only a small number of patients. Adverse effects were reported in studies using 13-*cis*-retinoic acid (1–2 mg/kg/day), and high-dose vitamin A (300,000 IU per week) (Lodi et al 2006).

Asthma

A study evaluated serum vitamin A concentrations in 26 well-nourished Japanese children with asthma (mean age of 5.5 years) with C-reactive protein (CRP) concentration <0.6 mg/dL, to exclude the acute phase response. Mean serum vitamin A concentrations were significantly lower in asthmatic children compared to controls, and there was also a significant correlation between CRP and serum vitamin A concentrations in children with asthma (Mizuno et al 2006). This observation was also reported in a case–control study involving 96 subjects which found low serum levels of vitamin A (and lycopene) were associated with an increased risk of bronchial asthma (Riccioni et al 2007). Whether low vitamin A status plays a role in chronic inflammatory processes within the lung

or is reduced as a consequence of long-term disease remains to be tested further.

Lung function in cystic fibrosis (CF)

Patients with CF may have impaired absorption of fat-soluble vitamins such as vitamin A. Some studies indicate vitamin A status is associated with respiratory health in patients with CF. Whether supplemental vitamin A has any benefits in CF is still speculative. A Cochrane systematic review did not find any eligible randomised or quasi-randomised controlled trials, and could not provide any firm conclusions on the effects (beneficial or harmful) of supplementation with vitamin A (O'Neil et al 2008). Previously, a small study involving 38 patients with stable CF (mean age of 15.3 years) found a significant correlation between serum vitamin A concentrations and lung function measurements including forced expiratory volume in 1 s, forced vital capacity and peak expiratory flow (Aird et al 2006). Similarly, a retrospective study found CF patients with reduced vitamin A and E levels (even within the normal range) had increased incidence of pulmonary exacerbations (evaluated by a scale of clinical status including symptoms and chest examination findings) (Hakim et al 2007). It is possible the antioxidant activity of vitamin A reduces oxidative damage to lung tissues and in this way provides some protection in CF. Whilst patients with CF and pancreatic insufficiency are at increased risk of deficiency of fat-soluble vitamins including vitamin A, two studies examining vitamin A status in CF patients found CF patients had higher intake and serum retinol levels compared to those without CF (Graham-Maar et al 2006, Maqbool et al 2008). Monitoring may be required to prevent excessive vitamin A supplementation.

Osteoporosis

Whether high-dose vitamin A supplementation increases the risk of osteoporosis remains unclear.

Evidence supporting the association comes from cell studies, animal studies and some but not all human observational studies. Four large, prospective observational studies reported a positive association between vitamin A intake and osteoporosis and fracture rates (Melhus et al 1998, Feskanich et al 2002, Promislow et al 2002, Michaelsson et al 2003). These studies suggested that the amount needed to reduce bone density may be as low as 1500 retinol equivalents (RE), although vitamin A is normally regarded as safe in amounts up to 3000 RE (Penniston & Tanumihardjo 2006). In contrast, numerous studies have failed to find a significant association (Sowers & Wallace 1990, Houtkooper et al 1995, Kawahara et al 2002, Kaptoge et al 2003, Rejnmark et al 2004, Barker et al 2005, Wolf et al 2005). In a study comparing vitamin A intake, serum vitamin A and bone turnover markers in postmenopausal women, no statistical differences were found between those with osteoporosis compared with those without (Penniston et al 2006). The inconsistency in results may be partly due to the difficulty in accurately assessing vitamin A intake and status, as well as the multiple variables influencing bone health (Ribaya-Mercado & Blumberg 2007).

Anaemia

Vitamin A and iron are inter-dependent nutrients, with iron required for the metabolism of vitamin A and maintenance of circulating levels of retinol; and vitamin A required for the mobilisation of iron from its stores for use in haemoglobin synthesis. Some studies have found improving vitamin A status in deficient individuals improves anaemia (Zimmermann et al 2006, Berger et al 2007, Hyder et al 2007). In a double-blind, randomised trial, 81 children (77% with low vitamin A status) received either vitamin A (200,000 IU) or placebo at baseline and again after 5 months. After 10 months, compared to the placebo group, the vitamin A-treated group had increased levels of retinol, increased haemoglobin and mean corpuscular volume and decreased the serum transferrin receptors indicating improved iron-deficient erythropoiesis. Prevalence of anaemia in the treated group decreased from 54% to 38%. Ferritin levels in the vitamin A group were also decreased, suggesting vitamin A increased mobilisation of hepatic iron stores (Zimmermann et al 2006). In a study comparing the impact of vitamin A on the health of children aged 12–59 months in rural Indonesia, it was found that those who had not received their vitamin A treatment in the previous 6 months were significantly more likely to be anaemic, underweight, wasted, and have higher rates of diarrhoea and fever than children who received vitamin A (Berger et al 2007).

Alternatively, some studies found no association between iron deficiency and vitamin A. In a randomised controlled trial in central Africa, 700 pregnant women (2–24 weeks gestation) with haemoglobin <11.0 g/dL were treated with either vitamin A (5000 IU or 10,000 IU) or placebo, plus iron (60 mg elemental iron as ferrous sulfate), folate (0.25 mg), and sulfadoxine/pyrimethamine for antimalarial prophylaxis until delivery. Whilst women in the vitamin A-treated groups were less likely to have depleted vitamin stores at the end of the pregnancy, there were no significant differences in anaemia, severe anaemia and iron status compared with the placebo group. This population was thought to be less vitamin A deficient compared with Asian countries such as Indonesia and Nepal where positive results have previously been found (van den Broek et al 2006). Similarly, a randomised, placebo-controlled trial conducted with mothers and their infants in Zimbabwe observed no effect on haemoglobin or anaemia levels evaluated 8–14 months after supplementation (400,000 for mothers and 50,000 IU for infants) (Miller et al 2006). In a double-blind trial involving HIV-1-infected pregnant women from Tanzania, subjects were randomised to receive daily supplements of 30 mg beta-carotene + 5000 IU preformed vitamin A only; multivitamins (vitamins B, C and E), preformed vitamin A and beta-carotene plus multivitamins, or placebo. All women also received iron and folate supplements during pregnancy. Whilst

haemoglobin concentrations significantly improved in women in the multivitamin group and their children, those in the beta-carotene and vitamin A only group did not significantly differ from placebo (Fawzi et al 2007).

Mortality risk

In a Cochrane systematic review, the effect of antioxidant supplements on mortality in primary or secondary prevention randomised clinical trials was evaluated; vitamin A used as sole treatment or in combination with other antioxidants (15 trials, mean dose of 20,219 IU) had no significant effect on mortality. In fact, after excluding the high-bias risk trials analysis found vitamin A significantly increased mortality in five trials (Bjelakovic et al 2008). This finding requires further investigation to confidently rule out the possible effect of confounders.

OTHER USES

Vitamin A has also been used in the treatment of menorrhagia and premenstrual syndrome (PMS), to prevent glaucoma and cataract, Crohn's disease, sinusitis and rhinitis.

DOSAGE RANGE

- Vitamin A activity is expressed as a unit called microgram RE (Miller et al 1998): 1 microgram RE = 1 microgram all-trans retinol or 6 microgram all-trans beta-carotene or 3.33 international units (IU) of vitamin A or 1 microgram RE is equivalent in activity to 1.78 microgram of retinyl palmitate and 10 IU activity from beta-carotene.

Recent changes to the Therapeutic Goods Act regarding vitamin A require the following statement be included on the labels of vitamin A preparations for internal use:

1. 'The recommended adult daily intake of vitamin A from all sources is 700 microgram RE (2330 IU) for women, and 900 microgram RE (3000 IU) for men.
2. WARNING — when taken in excess of 3000 microgram RE daily, vitamin A may cause birth defects.
3. If you are pregnant, or considering becoming pregnant, do not take vitamin A supplements without consulting your doctor or pharmacist'.

Australian recommended daily intake (RDI) (in micrograms RE)

Children
1–3 years: 300 microgram/day.
4–8 years: 400 microgram/day.
9–13 years: 600 microgram/day.
Girls, 14–18 years: 700 microgram/day.
Boys, 14–18 years: 900 microgram/day.
Adults
Females: 700 microgram/day.
Males: 900 microgram/day.
Upper level of intake: 3000 microgram/day.
Pregnancy
<18 years: 700 microgram/day.
>18 years: 800 microgram/day.
Lactation: 1100 microgram/day.

Clinical note — Vitamin A toxicity in two young children

In 2001, a report of two children admitted to hospital with symptoms of vitamin A toxicity was published in the *Medical Journal of Australia*. One case involved a 2-year-old girl with anorexia, lethargy and leg pain, an erythematous rash over her back and elbows and irritability. All symptoms resolved over 2 weeks following withdrawal of the supplement. The second case involved a child who had previously been prescribed oral etretinate by a dermatologist (for an unspecified period of time), which was ceased 3 months prior to vitamin A supplementation. In both cases, the dose of vitamin A taken was in excess of that provided by standard over the counter (OTC) products (Coghlan & Cranswick 2001).

- Deficiency without corneal changes: 10,000–15,000 IU/day for 1–2 weeks, until clinical improvement is apparent.
- General treatment doses: 10,000–50,000 IU/day have been used short term.

According to clinical studies

- Reducing secondary infection in children with measles: 200,000 IU of vitamin A on 2 consecutive days when vitamin A deficiency may be present.
- Retinitis pigmentosa: 15,000 IU/day.

TOXICITY

Cumulative toxicity is possible when doses greater than 100,000 IU are ingested long term. Acute toxicity is very difficult to induce in adults, as doses above 2,000,000 IU are required (Hendler et al 2001).

Early signs of toxicity include dry rough skin, cracked lips, coarse hair, sparse hair, alopecia of eyebrows, diplopia, dryness of the mucous membranes, desquamation, bone and joint pain, fatigue and malaise, nausea and vomiting and psychological changes mimicking depression and schizophrenia.

Later signs include irritability, increased intracranial pressure and headache, dizziness, liver cirrhosis, fibrosis and cirrhosis, vomiting, haemorrhage and coma (Miller et al 1998).

People with chronic renal disease typically have elevated plasma retinol levels and therefore may be at greater risk of toxicity if supplementation is used.

It is important to note that beta-carotene is not associated with teratogenic effects or vitamin A toxicity and is considered a far safer nutrient.

ADVERSE REACTIONS

In general, doses of vitamin A that do not exceed physiological requirements have no adverse effects.

SIGNIFICANT INTERACTIONS

Chemotherapeutic agents

Adjunctive treatment may improve drug response — consider individual patient characteristics, form and presentation of cancer, drugs used before administration — use only under professional supervision.

Cholestyramine
Reduces vitamin A absorption — increase dietary intake of vitamin A-rich foods or consider supplementation with long-term use.

Colchicine
Colchicine may interfere with vitamin A absorption and homeostasis — co-administer for beneficial interaction.

HMG-CoA reductase inhibitor drugs (statins)
These drugs increase the serum levels of vitamin A, the clinical significance of which is unclear — observe patients taking this combination (Muggeo et al 1995).

Isotretinoin
Toxicity may be increased — avoid this combination.

Minocycline
Long-term vitamin A use with this drug increases the risk of pseudotumour cerebri — use with caution.

Oral contraceptives
Increased vitamin A levels occur in oral contraceptive pill (OCP) users due to longer storage in the liver (Tyrer 1984) — use caution with large doses of retinol.

Orlistat
Reduces vitamin A levels — increase dietary intake of vitamin A-rich foods or consider supplementation with long-term use.

Tetracyclines
Adjunctive use may increase side effects such as headaches, pseudotumour cerebri — avoid.

CONTRAINDICATIONS AND PRECAUTIONS
Doses greater than 10,000 IU/day long term should be used with caution.

People with liver or renal disease, alcoholism or severe osteoporosis should use vitamin A supplements with caution.

PREGNANCY USE
In the USA, sources state that doses up to 10,000 IU/day are safe in pregnancy, but Australian authorities recommend that supplements containing ≥2500 IU of vitamin A per dose must have pregnancy warning statements on their labels.

It is important to note that beta-carotene, found naturally in plants, is not associated with teratogenic effects or vitamin A toxicity.

The teratogenicity of 13-*cis*-retinoic acid, a synthetic derivative of vitamin A available in Australia as Roaccutane, is well established and that substance is contraindicated in pregnancy.

PATIENTS' FAQs
What will this vitamin do for me?
Vitamin A is essential for health and is involved in many different biochemical processes in the body. Some research has suggested that it reduces the incidence and severity of some infectious diseases in children. Vitamin A or its synthetic derivatives have also been used in many skin conditions such as acne, psoriasis, UV-induced skin damage and photo-ageing and the treatment of some cancers.

When will it start to work?
This will depend on the form of vitamin A being used and the indication it is being used to treat.

Are there any safety issues?
Taking high doses of vitamin A long term can cause side effects and is contraindicated in pregnancy.

PRACTICE POINTS/PATIENT COUNSELLING
- Vitamin A is a fat-soluble antioxidant that is chiefly stored in the liver.
- It is involved in maintaining vision, healthy immune function, necessary for growth and development, reproductive capability and healthy epithelial cell function.
- It is used to treat and prevent deficiency states, and there is clinical evidence that supplementation reduces the incidence and severity of infections during childhood, particularly measles and infectious diarrhoea, reduces the incidence of croup and otitis media in children with measles, and may be useful in retinitis pigmentosa.
- Vitamin A deficiency is widespread in some countries, increasing the risk of childhood infectious disease, mortality and deficiency-associated blindness.
- Excessive vitamin A supplementation can induce a toxicity state that can have serious, sometimes irreversible consequences.

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Vitamin B_1

HISTORICAL NOTE The Chinese medical book 'Neiching' describes beriberi in 2697 BC, but it was not known for a long time that vitamin B_1 deficiency was responsible. In 1926, two Dutch chemists isolated anti-beriberi factor from rice bran extracts and in the 1930s its structure was determined.

BACKGROUND AND RELEVANT PHARMACOKINETICS

Vitamin B_1 is a water-soluble compound required by all tissues. It is also known as thiamine, anti-beriberi factor, antineuritic factor and its active coenzyme form: thiamine diphosphate. Thiamine's phosphate ester functions as a coenzyme in carbohydrate metabolism and nerve conduction. The free form is found in plasma, but intracellularly it is phosphorylated to one of three forms: thiamine monophosphate (TMP), thiamine diphosphate (TDP) or thiamine triphosphate (TTP), with the majority as TDP, which is the most active form. The ability of thiamine to shift between these different levels of phosphorylation makes it a key nutrient in energy pathways.

There are two sources of thiamine: dietary and a bacterial source whereby it is synthesised by the normal intestinal microflora. Thiamine is absorbed from the small intestine by a saturable rate-limiting transport mechanism. The absorption of thiamine in the gastrointestinal tract can be impaired by the presence of naturally occurring thiaminases that are found in raw fish or polyhydroxyphenols found in certain food and beverages; for example, coffee, tea, blueberries, red cabbage and brussel sprouts (Groff & Gropper 2009).

It is transported by the portal circulation to the liver where it is metabolised, then excreted mainly through the kidneys. Thiamine is found in high concentrations in skeletal muscle, heart, liver, kidneys and brain and its half-life is approximately 15 days (Singleton & Martin 2001).

CHEMICAL COMPONENTS

Thiamine (vitamin B_1) is a water-soluble substance, consisting of thiazole and pyrimidine rings joined by a methylene bridge.

FOOD SOURCES

Brewer's yeast, lean meat and legumes are considered the richest sources of thiamine. Other sources include cereals, grains, pasta, wheat germ, soy milk, seeds and peanuts.

It is possible to lose up to 85% of the thiamine content in meat through cooking and canning, and up to 60% from cooking vegetables (Tanphaichitr 1999). There is also loss through refining of grains and in some countries, the fortification of wheat flour with B vitamins is mandatory to compensate for this loss.

DEFICIENCY SIGNS AND SYMPTOMS

The body only stores a small amount of thiamine and signs of deficiency tend to develop within 15–18 days of restricted intake.

Beriberi is the classic thiamine deficiency state. General early deficiency signs and symptoms include fatigue, weakness, rigidity (due to corresponding increase in lactic acid production), irritability, poor memory, sleep disturbances, chest wall pain, anorexia, abdominal discomfort and constipation.

There are three forms of beriberi: dry, wet and cerebral, also known as Wernicke–Korsakoff syndrome. Dry beriberi is associated with peripheral neurological changes, whereas cerebral beriberi involves alterations to ocular function, cognitive function secondary to bilateral symmetrical brain lesions in the paraventricular grey matter, producing ataxia, which can also be fatal. In addition to neurological changes, wet beriberi is associated with cardiovascular changes characterised by peripheral vasodilation, sodium and water retention, increased cardiac output and myocardial failure, which can advance to become fatal in severe cases. Although

alcoholism is the major cause of Wernicke–Korsakoff syndrome, it has also been reported in several other conditions such as hyperemesis gravidarum, hyperemesis due to gastroplasty, hyperthyroidism and inadequate parenteral nutrition (Bonucchi et al 2008, Gardian et al 1999, Ogershok et al 2002, Seehra et al 1996, Spruill & Kuller 2002, Tan & Ho 2001, Togay-Isikay et al 2001, Toth & Voll 2001). A recent case report of thrombocytopenia in a patient with Wernicke–Korsakoff syndrome, responsive to thiamine repletion, has introduced the possibility that this may constitute an unusual feature of the deficiency picture (Francini-Pesenti et al 2007).

Primary deficiency

Primary deficiency is caused by inadequate dietary intake of thiamine, particularly in people subsisting mainly on highly polished rice (de Montmollin et al 2002) or unfortified grain products. Insufficient intake may also occur in anorexia and in people receiving total parenteral nutrition (TPN) without supplemental thiamine.

Secondary deficiency

Secondary deficiency is caused by an increased requirement, as in hyperthyroidism, pregnancy, lactation, fever, acute infection, increased carbohydrate intake, folate deficiency, malabsorption states, hyperemesis, prolonged diarrhoea, strenuous physical exertion, breastfeeding, adolescent growth and states of impaired utilisation such as severe liver disease, alcoholism, chronic haemodialysis, diabetes (types 1 and 2) and people taking loop diuretics long term. Additionally, pyruvate dehydrogenase deficiency can result in deficiency (Beers & Berkow 2003, Wahlqvist et al 2002, Thornalley et al 2007, Wardlaw et al 1997). Alternatively, latent primary thiamine deficiencies produce overt clinical features when the patient is exposed to thiamine metabolism stressors, such as those listed above, e.g. pregnancy, surgery etc (Al-Nasser et al 2006).

> ***Clinical note — Thiamine deficiency is not uncommon***
>
> Several observational studies have reported that thiamine deficiency is not uncommon in the elderly. A study of 118 elderly hospital patients identified a moderate deficiency incidence of 40% (Pepersack et al 1999). Similar results were obtained in another survey where marginal thiamine deficiency had an incidence of 31% and frank deficiency of 17% (O'Keeffe et al 1994). The importance of including thiamine deficiency in the diagnostic work-ups of at-risk individuals is underscored by the high mortality rate in Wernicke–Korsakoff syndrome (10–20%), reported to be directly the result of under-diagnosis (Bonucchi et al 2008). Similarly, it is important to keep in mind that there is significant inter-individual variability in both susceptibility to thiamine deficiency and its consequences (Al-Nasser et al 2006).
>
> Besides inducing deficiency signs and symptoms, preliminary research suggests that inadequate intake could increase susceptibility to neurodegeneration, particularly in aged organisms (Nixon et al 2006, Pitkin & Savage 2004).

MAIN ACTIONS

Coenzyme

Carbohydrate and branched-chain amino acid metabolism

Thiamine serves as a cofactor for several enzymes involved in carbohydrate catabolism, including pyruvate dehydrogenase, transketolase and alpha-ketoglutarate, and for the branched-chain alpha-keto acid dehydrogenase complex that is involved in amino acid catabolism (Singleton & Martin 2001). Some of these enzymes are also important in brain oxidative metabolism (Molina et al 2002).

Neurotransmitter biosynthesis

Thiamine is involved in the biosynthesis of a number of cell constituents, including the neurotransmitters acetylcholine and gamma aminobutyric acid (GABA).

DNA

Thiamine is involved in the synthesis of precursors of DNA, therefore thiamine use is increased in tumours.

Neuropsychological actions

Besides its involvement in neurotransmitter biosynthesis, thiamine is required for neurotransmission, nerve conduction, blood cerebrospinal fluid (CSF) barrier (BCSFB) functionality and muscle action. In the form of TTP, it concentrates in nerve and muscle cells and activates membrane ion channels. As such, thiamine deficiency is associated with neurological changes and suspected of contributing to the development of alcoholic peripheral neuropathy and Wernicke–Korsakoff's syndrome from a variety of aetiologies (D'Amour et al 1991, Nixon et al 2006). The most recent evidence from animal studies suggests that impaired BCSFB function, secondary to thiamine deficiency, allows passage of neuroactive substances into the brain, damaging the choroid plexus (Nixon et al 2006).

CLINICAL USE

Many of the clinical uses of thiamine supplements are conditions thought to arise from a marginal deficiency, but some indications are based on the concept of high-dose supplements acting as therapeutic agents. In practice, vitamin B_1 is usually recommended in combination with other B-group vitamins.

Deficiency: treatment and prevention

Thiamine supplements are traditionally used to treat or prevent thiamine deficiency states in people at risk (see *Secondary deficiency*).

Hyperemesis

Although thiamine supplementation will not reduce the symptoms of hyperemesis, it may be necessary in cases of hyperemesis gravidarum and hyperemesis due to gastroplasty in order to avoid deficiency states and the development of Wernicke's encephalopathy, which has been reported in these situations, although noted to be a rare consequence. It may be precipitated in part by intravenous fluids containing dextrose, and is more commonly seen when the patient's liver transaminases are elevated, which may contribute to the encephalopathy (Francini-Pesenti et al 2007, Gardian et al 1999, Seehra et al 1996, Spruill & Kuller 2002, Tan & Ho 2001, Togay-Isikay et al 2001, Toth & Voll 2001, Welsh 2005).

Alcoholism

In alcoholism, a state of decreased intake, absorption, utilisation and increased requirement for thiamine occurs, necessitating increased intakes to avoid deficiency states (D'Amour et al 1991). In cases of Wernicke's encephalopathy, monitoring of thiamine status and prophylactic intravenous treatment will inhibit the progression to Korsakoff's psychosis (Thomson & Marshall 2005). Ongoing research has revealed that the cerebellar neurotoxicity associated with excess alcohol is more likely mediated predominantly by thiamine deficiency than by direct ethanol cytotoxicity, as previously believed (Mulholland et al 2005); however, there is growing evidence of a strong negative synergy between the two that extends well beyond the increased need for thiamine as a result of alcohol consumption (Nixon et al 2006).

Total parenteral nutrition

Several case reports show that patients who have received TPN without proper replacement of thiamine are at risk of developing deficiency signs and Wernicke's encephalopathy (Francini-Pesenti et al 2007, Hahn et al 1998, van Noort et al 1987, Vortmeyer et al 1992, Zak et al 1991). Recent preliminary evidence suggests that current TN vitamin formulations are not sufficient to ensure thiamine repletion in all patients (Francini-Pesenti et al 2008).

Hyperthyroidism

Although a somewhat rare sequelae, a handful of case reports describe Wernicke–Korsakoff's syndrome in patients suffering thyrotoxicosis (Bonucchi et al 2008).

Surgical patients

Several recent case reports detailing Wernicke's encephalopathy in surgical patients highlight why this patient group should be considered 'high risk' for thiamine deficiency: malnutrition, high stress levels, vomiting and ileus, which together increase thiamine requirements substantially (Al-Nasser et al 2006, Francini-Pesenti et al 2007. Several authors suggest that thiamine deficiency may be latent in the preoperative patient, with surgery or postoperative TPN precipitating clinical manifestation and consequently recommend preoperative screening for thiamine status (Al-Nasser et al 2006.

Acute alcohol withdrawal

Several guidelines for the support of alcohol withdrawal recommend a dose of 100 mg thiamine administered intravenously or intramuscularly before routine administration of dextrose-containing solutions (Adinoff et al 1988, Erstad & Cotugno 1995).

Alzheimer's dementia (AD)

Thiamine status has been investigated and found, amongst other nutrients, to have an inverse relationship with cognitive function in the elderly (Nourhashemi et al 2000). More specifically, AD has been associated with reduced plasma levels of thiamine, according to several clinical studies (Gold et al 1995, 1998, Molina et al 2002). One study analysed cerebral cortex samples from autopsied patients with AD and found slight reductions in TDP levels compared with matched controls (Mastrogiacoma et al 1996). Others have demonstrated reduced activities of thiamine-dependent enzymes, together with a strong correlation between these reductions and the extent of the dementia in autopsied brains (Gibson & Blass 2007).

Proposed mechanisms for the relationship between thiamine and AD are varied, ranging from its role as an antioxidant and its critical contribution to the Krebs cycle to its involvement in the production of acetylcholine, disturbances of which have all been implicated in AD pathology (Bubber et al 2004, Butterfield et al 2002, Gibson & Blass 2007, Kruse et al 2004). Recent animal research points towards the shared features of thiamine deficiency and AD pathology in the brain, in particular, with increased oxidative stress and inflammation precipitating neuronal loss in specific brain areas and concomitant promotion of plaque formation (Karuppagounder et al 2008).

Investigation with high-dose thiamine supplementation in this population has produced mixed results (Blass et al 1988, Meador et al 1993, Mimori et al 1996). One double-blind, placebo-controlled, crossover study showed that a dose of 3000 mg thiamine/day produced higher global cognitive ratings as assessed by the Mini-Mental State Examination compared with a niacinamide placebo. However, there were no changes to clinical state and behavioural ratings (Blass et al 1988). Another clinical study of unknown design found positive results with a dose ranging between 3 and 8 g/day of thiamine (Meador et al 1993), whereas a long-term study using high-dose supplementation produced negative results (Mimori et al 1996).

Although promising overall, a 2001 Cochrane review stated that it is still not possible to draw any conclusions about the effectiveness of thiamine supplementation in AD (Rodriguez-Martin et al 2001). In practice, it is often used as part of a broad-spectrum approach with other B-group vitamins in age-related cognitive decline; however,

further research is required to determine whether this method produces more consistent results, particularly as an adjunct to standard pharmaceutical treatments (Gibson & Blass 2007).

Congestive heart failure (CHF)

A 2001 review concluded that there was insufficient evidence from large trials to confirm thiamine as a corrective treatment in CHF; however, prophylactic supplementation was worthwhile, considering the high prevalence of deficiency in this population (Blanc & Boussuges 2001). The largest and most recent trial since then was published in 2006 and confirmed that the incidence of deficiency is notable amongst CHF patients (Hanninen et al 2006). It is suspected that patients with existing heart failure are at increased risk of thiamine deficiency because of diuretic-induced depletion, advanced age, malnutrition and/or periods of hospitalisation.

A number of small interventional studies have assessed the effect of thiamine supplementation in patients with CHF with promising results. In one pilot study six patients treated with IV thiamine, such that their thiamine status returned to normal, resulted in increased left ventricular ejection fraction (LVEF) in four of five patients studied by ECG (Seligmann et al 1991). A randomised, placebo-controlled, double-blind study of 30 patients compared the effects of IV thiamine (200 mg/day) to placebo over 1 week followed by oral thiamine (200 mg/day) taken for 6 weeks. In the 27 patients completing the full 7-week intervention, LVEF rose by 22%. Other positive results have been reported from similar studies (Hanninen et al 2006). The current position of key researchers in this area is that, together with other micronutrients critical for myocardial energy production and control of oxidative stress (e.g. taurine), thiamine inadequacy is likely to exacerbate myocyte dysfunction and loss in this condition, making repletion an important therapeutic objective (Allard et al 2006).

Diabetes

Given thiamine's essential role in the key carbohydrate metabolic enzymes: transketolase, pyruvate dehydrogenase and alpha-ketoglutarate dehydrogenase and the precipitation of glucose toxicity secondary to thiamine deficiency (Nixon et al 2006), there is growing interest in the therapeutic potential of this nutrient in diabetes. Preliminary research of thiamine status in diabetic patients reveals significantly high rates of deficiency (≈75% of type 1 and 2 diabetics), secondary to greatly increased renal losses of this B vitamin (Thornalley et al 2007). These initial findings lead researchers to speculate that reduced thiamine availability may exacerbate diabetic metabolic dysfunction, particularly with respect to microvascular complications. Adding to the evidence of earlier in vitro studies demonstrated that thiamine improves endothelial function, while protecting against insulin-mediated vascular smooth muscle cell proliferation (Arora et al 2006).

A recent investigation into high-dose thiamine (100 mg taken three times daily) over 3 months in small sample of type 2 diabetes mellitus (T2DM) patients with microalbuminuria demonstrated reversal of early stage nephropathy in the treatment group, without altering glycaemic control, dyslipidaemia or blood pressure (Rabbani et al 2008). Another study employing thiamine, this time in IV form, improved endothelium-dependent vasodilation in hyperglycaemic patients (both diabetic and non-diabetic); however, the mechanism of action remains unclear (Arora et al 2006).

The assessment of thiamine adequacy in diabetic patients is confounded by the invalidity of standard diagnostic tests, e.g. red blood cell transketolase activity (Thornalley et al 2007).

Dysmenorrhoea

A Cochrane review of herbal and dietary therapies for primary and secondary dysmenorrhoea concluded that thiamine is an effective treatment when taken at 100 mg/day, although this conclusion is tempered slightly by its basis on only one large RCT (Wilson & Murphy 2001). That trial was a randomised, double-blind, placebo-controlled, crossover design conducted over 5 months in 556 women and procured a positive improvement in >90% of the treatment cycle versus <1% in the placebo phase. The improvements observed during treatment appeared to have lasting effects, even after cessation of supplementation, for up to 3 months (Gokhale 1996). Due to the dramatic 'success' of this study, it has attracted scepticism regarding its methodology; certainly a question is why, with such positive results, an attempt to replicate the findings has not been undertaken in over 9 years (Fugh-Berman & Kronenberg 2003).

OTHER USES

Cataracts

A case-controlled study of 72 patients found that thiamine supplementation reduced the incidence of cortical, nuclear and mixed cataracts (Leske et al 1991).

Coma

A general approach to patients presenting to hospital with coma is to ensure adequate oxygenation, blood flow and treatment with hypertonic glucose and thiamine (Alguire 1990, Buylaert 2000).

Epilepsy

A randomised, placebo-controlled study involving 72 patients with epilepsy who had received long-term phenytoin treatment alone or in combination

Clinical note — No protection against insect bites

One claim that has been around for many years is that high oral doses of certain B vitamins could act as a deterrent to insects such as mosquitoes. Principally, the myth has centred on thiamine. A recent review of prophylaxis against insect bites found that neither topical application nor oral dosing of thiamine is an effective preventative strategy (Rudin 2005).

with phenobarbital found that administration of thiamine (50 mg/day) over 6 months improved neuropsychological functions in both verbal and non-verbal IQ testing (Botez et al 1993). This study also found both folate supplementation and placebo ineffective.

Fatigue
B-group vitamins are often taken by the public to lessen the impact of 'stress' and provide an energy boost. In one study, thiamine 10 mg/day significantly increased appetite, energy intake, body weight, general wellbeing and decreased fatigue, compared with placebo in a group of 80 randomly chosen women from a population with known marginal deficiency (Smidt et al 1991). Thiamine supplementation also tended to reduce daytime sleep time, improve sleep patterns and increase activity.

HIV
Several neuropathological reports have described brain lesions characteristic of Wernicke's encephalopathy in patients with AIDS. One study found a 23% prevalence of thiamine deficiency in AIDS patients with no history of alcohol abuse (Butterworth et al 1991).

Neurogenic impotence
A dose of 25 mg thiamine taken orally resulted in normalisation of erection in a man with a history of chronic alcoholism and erectile dysfunction of 1 year's duration (Tjandra & Janknegt 1997). However, more recent evidence discussing the causes of neurogenic impotence suggests that thiamine deficiency is relatively rare (Finsterer 2005).

Maple syrup urine disease
Of four paediatric patients with maple syrup urine disease, three responded to thiamine therapy with a reduction in concentration of plasma and urinary branched-chain amino and keto acids (Fernhoff et al 1985).

Optic neuropathy
Several case reports suggest this condition can be caused by thiamine deficiency and successfully treated with supplementation. One case report of a man developing optic neuropathy as a result of receiving TPN without thiamine for 4 weeks found that supplementation with thiamine reversed the condition (Suzuki et al 1997). Two cases of symmetrical, bilateral optic neuropathy associated with thiamine deficiency were successfully treated with thiamine supplementation (Hoyt & Billson 1979).

DOSAGE RANGE
- Prevention of deficiency (adult Australian RDI): 1.1–1.2 mg/day.
- Treatment of marginal deficiency states: 5–30 mg/day.
- Critical deficiency: 50–100 mg IV or IM for 7–14 days, after which oral doses are used (Tanphaichitr 1999).
- CHF: 100 mg twice daily IV for 1–2 weeks, then 200 mg/day orally.
- Dysmenorrhoea: 100 mg/day orally.
- Support of alcohol withdrawal: 100 mg given IV or IM.
- Fatigue (when marginal deficiency likely): 10 mg/day.
- Type 2 diabetes mellitus: 100 mg three times daily.

Australian RDI
Females >13 years: 1.1 mg/day.
Males >13 years: 1.2 mg/day.

TOXICITY
Toxicity does not occur with oral thiamine as it is rapidly excreted by the kidneys (Tanphaichitr 1999), although there is some evidence that toxicity can occur with very large doses given parenterally (Jacobs & Wood 2003).

ADVERSE REACTIONS
Thiamine is well tolerated.

SIGNIFICANT INTERACTIONS

Antibiotics
Antibiotics can reduce the endogenous production of B-group vitamins by gastrointestinal flora, theoretically resulting in lowered B vitamin levels. The clinical significance of this is unclear — increase intake of vitamin B_1-rich foods or consider supplementation.

Iron
Iron precipitates thiamine, thereby reducing its absorption — separate doses by 2 h.

Loop diuretics
Chronic use may result in lowered levels of vitamin B_1 — increase intake of vitamin B_1-rich foods or consider long-term supplementation.

Other B vitamins
Thiamine deficiency commonly occurs in conjunction with poor B_2 and B_6 status (Jacobs & Wood 2003).

Sulfites
Concomitant intake may inactivate thiamine, which has been reported in TPN solutions (Bowman & Nguyen 1983).

Tannins
Tannins precipitate thiamine, thereby reducing its absorption — separate doses by 2 hours.

CONTRAINDICATIONS AND PRECAUTIONS

Cancer
There is some evidence of thiamine being associated with nucleic acid ribose synthesis of tumour cells in its biologically activated form (Boros 2000). As such, thiamine may theoretically increase tumour formation. To date, the clinical relevance of this finding has not been explored.

PRACTICE POINTS/PATIENT COUNSELLING

- Thiamine is necessary for healthy functioning and is involved in carbohydrate and protein metabolism, the production of DNA and several neurotransmitters and nerve and muscle functions.
- Supplements are used to treat deficiency or prevent secondary deficiency in people at risk (e.g. alcoholism, malabsorption syndromes, hyperemesis, chronic diarrhoea, hyperthyroidism, pregnancy, lactation, fever, acute infection, folate deficiency, strenuous physical exertion, breastfeeding, adolescent growth, severe liver disease and chronic use of loop diuretics). There is a higher incidence of deficiency in people with CHF; however, it is not known whether correction of the deficiency will improve disease symptoms.
- High-dose thiamine supplements relieve symptoms of dysmenorrhoea, according to one large RCT.
- Additionally, some early research has found an association between Alzheimer's dementia and low plasma thiamine levels, with supplementation producing some benefits; however, further investigation is still required.
- Oral supplements are non-toxic, but should be used with caution in patients with cancer.

PREGNANCY USE

Safe during pregnancy and lactation.

PATIENTS' FAQs

What will this vitamin do for me?

Thiamine is necessary for healthy functioning and is involved in carbohydrate and protein metabolism, the production of DNA, several brain chemicals and nerve and muscle functions. Supplements are taken to avoid deficiency states that can occur, for instance, in alcoholism, extreme vomiting, chronic diarrhoea or malabsorption syndromes. In high doses, it may relieve symptoms of painful menstruation and may be a useful adjunct in CHF.

When will it start to work?

Thiamine supplements can have dramatic effects on deficiency states within 24 h. The response time for other conditions, such as dysmenorrhoea and CHF, also appears to be reasonably fast. Within two menstrual cycles, supplementation produced marked reductions in dysmenorrhoea, and CHF patients treated for only 7 weeks showed positive responses.

Are there any safety issues?

Taken orally, thiamine is considered non-toxic. People with cancer should consult with their physician before taking high-dose thiamine supplements.

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Vitamin B_2 — riboflavin

BACKGROUND AND RELEVANT PHARMACOKINETICS

Riboflavin is a water-soluble B-group vitamin that is sensitive to light and alkali conditions. Once absorbed, it is converted into its active form. Riboflavin works as a component of two primary coenzymes, flavin adenine dinucleotide (PAD) and flavin mononucleotide (FMN). Both of these belong to the class known as the flavin coenzymes, all of which are active in redox reactions involving hydrogen transfer and consequently important for the body's production of adenosine triphosphate (ATP). Although some organs (such as the liver) have relatively high concentrations of flavin coenzymes, the flavin seems to be present as coenzyme moieties of flavin holoenzymes, which are fully functional.

There are two sources of riboflavin: dietary and bacterial, whereby the vitamin is produced by normal gastrointestinal microflora. The amount of bacterially synthesised riboflavin depends on the type of diet consumed, with higher synthesis resulting from intake of vegetable-based diets than from meat-based diets (Said 2004). For direct dietary sources, see *Food sources* below.

Riboflavin uptake occurs mainly in the proximal part of the small intestine and involves a specialised, Na^+-independent carrier-mediated system. Adaptive changes alter the number and/or activity of carriers, and uptake is saturable when large pharmacological doses of riboflavin are ingested. There is evidence that bioavailability is optimal once 25 mg has been reached, and doses in excess of this show reduced or unaltered absorption efficacy

(Groff & Gropper 2009). The absorption of vitamin B_2 is enhanced when it is consumed in flesh foods and impeded by the presence of divalent metals (e.g. zinc, iron, copper and manganese).

FOOD SOURCES

The main food sources are organ meats, yeast products (including Vegemite), almonds, wheatgerm, wild rice and mushrooms. Vitamin B_2 is also found to a lesser extent in dairy products and vegetables. Maximum loss during cooking is 75% (Wahlqvist 2002).

DEFICIENCY SIGNS AND SYMPTOMS

Primary deficiency

Primary deficiency is associated with inadequate dietary intake, such as poor consumption of milk and other animal products. Primary deficiency is reported to be more common in the elderly and adolescent girls.

Secondary deficiency

Secondary deficiencies can develop in chronic diarrhoea, liver disease, chronic alcoholism, adrenal or thyroid hormone insufficiency, and postoperative situations in which total parenteral nutrition (TPN) solutions lack riboflavin. In most cases, riboflavin deficiency is accompanied by other vitamin deficiencies, such as deficiencies of vitamin B_6, niacin and folic acid. Drugs that impair riboflavin absorption or utilisation by inhibiting the conversion of the vitamin to the active coenzymes include tricyclic antidepressants, chemotherapy drugs and psychotropic agents. There is also evidence suggesting an apparent increase in riboflavin requirements with increased physical exercise.

Signs and symptoms of deficiency

The body's 'storage capacity' is sufficient to provide riboflavin for 2–6 weeks when nutritional status is normal, but during protein deficiency the stores are significantly reduced.

Initial symptoms of riboflavin deficiency are often non-specific and include: weakness, fatigue, mouth pain and personality changes. Isolated riboflavin deficiency seldom occurs and is usually associated with a deficiency of other B-group vitamins.

Other signs and symptoms are:

- angular stomatitis, cracked lips, cold sores and cheilosis
- glossitis, magenta tongue (Lo 1984)
- failure to grow in children
- ocular and visual disturbances, with symptoms such as burning, itching, sensitivity to light and conjunctivitis
- scaly and greasy dermatitis affecting the nasolabial folds, ears, eyelids, scrotum and labia majora (Lo 1984)
- desquamative dermatitis
- hair loss
- poor wound healing.

Of interest, a study of 154 pregnant women at increased risk of preeclampsia found that those who were riboflavin deficient were 4.7-fold more likely to develop the condition than those with adequate levels (Wacker et al 2000).

MAIN ACTIONS

Riboflavin is involved in many different biological processes and is essential for maintaining good health. It is involved in ATP production, is essential for immune function, tissue repair processes and general growth (it is required for the healthy growth of skin, nails and hair), and plays a key role in fatty acid oxidation and the metabolism of several other B vitamins.

Riboflavin has important antioxidant activity in itself, but also as part of the FAD-dependent enzyme glutathione reductase. It also activates vitamin B_6 and folate.

CLINICAL USE

A number of clinical trials have been conducted in which patients presenting with different condition have subsequently been found to have riboflavin deficiency. Treating the deficiency in some of these cases has been shown to improve the initial presenting condition.

Wound healing

Riboflavin deficiency lengthens the time to epithelialisation of wounds, slows the rate of wound contraction and reduces the tensile strength of incision wounds in vivo. Total collagen content is also significantly decreased, suggesting riboflavin deficiency will slow down wound-healing rate (Lakshmi et al 1989).

Migraine headaches: prophylaxis

Three clinical studies of varying design have found that treatment with high-dose riboflavin (400 mg) can reduce the frequency of migraine headaches; however, one double-blind study that used it in combination with magnesium and feverfew failed to show beneficial effects over low-dose riboflavin (25 mg).

The first was an open pilot study testing the effects of 400 mg riboflavin over 3 months in 49 patients. Active treatment produced positive results, with 59% of the treatment group experiencing a reduction in migraine frequency of at least 50% (Schoenen et al 1994). Based on these results, a second study with 55 subjects was conducted using a randomised, placebo-controlled design, with similar positive findings (Schoenen et al 1998). In 2004 an open-label study retested the same high dose of vitamin B_2 over 6 months and once again showed a significant reduction in headache frequency, from 4 days/month at baseline to 2 days/month after 3 and 6 months of treatment ($P < 0.05$). Use of abortive drugs reduced from 7 units/month to 4.5 units/month; however, the duration and intensity of each episode did not change significantly (Boehnke et al 2004).

Alternatively, a randomised, double-blind, controlled study using a combination of vitamin B_2 (400 mg), magnesium (300 mg) and feverfew (100 mg) failed to show benefits over riboflavin 25 mg. Both groups showed a comparable significant reduction in number of migraines, migraine day and migraine index; however, in neither group was frequency successfully reduced by more than 50%, which was the primary outcome (Maizels et al 2004). Interestingly, the response obtained was greater than the placebo response reported in other migraine prophylaxis trials.

Clinical note — Causes of migraine

Numerous theories exist to explain the underlying pathology of migraine headache. One theory proposes a deficit of mitochondrial energy metabolism, as patients with migraine show decreased brain mitochondrial energy reserve between attacks. Interestingly, patients with mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS) exhibit impaired mitochondrial energy metabolism, producing migraine-like headaches, which are in part ameliorated by prophylactic B_2 (Magis et al 2007).

Accordingly, riboflavin coenzyme Q10 and lipoic acid, as enhancers of mitochondrial energy efficiency, have been tested for prophylactic activity in migraine and appear to be promising agents (Magis et al 2007, Schoenen et al 1994). Recent studies in experimental models add to our knowledge of the actions of riboflavin in migraine, with confirmation that it produces antinociception and anti-inflammatory effects. The analgesic activity observed is independent of opioid mechanisms (Granados-Soto et al 2004).

Comparative trial

A clinical trial comparing riboflavin supplementation with standard beta-adrenergic antagonists found that both treatments significantly improved the clinical symptoms of migraine headache (Sandor et al 2000). Analysis of their effects on cortical potentials showed that the two treatments achieve these results by working through different mechanisms.

Age-related cataract prevention

Cataract was shown to be associated with riboflavin deficiency in animals in the 1930s and subsequently with deficiencies of amino acids, vitamins and some minerals (Wynn & Wynn 1996). This has been confirmed in human studies, in which lens opacities have been associated with lower levels of riboflavin, vitamins A, C and E, iron, and protein status (Leske et al 1995, Mares-Perlman et al 1995).

Glutathione reductase is a key enzyme involved in lens protection. Riboflavin levels indirectly influence glutathione reductase activity, increasing the ability of the lens to deal with free radical formation (Head 2001). One study documented severe glutathione reductase deficiency in 23% of human lens epithelium specimens, possibly reflecting a dietary deficiency of riboflavin (Straatsma et al 1991). Another study found that a significant number of people with cataracts have inactive epithelial glutathione reductase (Horwitz et al 1987).

A large cross-sectional survey of 2873 volunteers aged 49–97 years detected a link between dietary vitamin supplement and a lower incidence of both nuclear and cortical cataract. Vitamin A, niacin, riboflavin, thiamine, folate and vitamin B_{12} all appeared to be protective, either in isolation or as constituents of multivitamin preparations (Kuzniarz et al 2001).

A recent sample of 408 women from the Nurses' Health Study aged 52–74 years at baseline participated in a 5-year study that assessed nutrient intake and the degree of nuclear density (opacification).

Clinical note — Age-related cataract and antioxidants

Age-related cataract is an important public health problem, because approximately 50% of the 30–50 million cases of blindness worldwide result from leaving the condition untreated (Jacques 1999). The mechanisms that bring about a loss in transparency include oxidation, osmotic stress and chemical adduct formation (Bunce et al 1990). Besides traditional risk factors such as diabetes, nutrient deficiency is also being considered, particularly nutrients with antioxidant properties.

Findings revealed that the geometric mean 5-year change in nuclear density was inversely associated with the intake of riboflavin ($P = 0.03$) and thiamin ($P = 0.04$), and most significantly with the duration of vitamin E supplement use ($P = 0.006$) (Jacques et al 2005).

The evidence currently suggests that higher intakes of riboflavin protect against the progression of age-related lens opacification.

Breast cancer — adjunctive treatment to tamoxifen

Riboflavin's importance is recognised in a range of terminal disease states, most notably in breast cancer, where its cellular absorption is significantly enhanced (Bareford et al 2008). Based on its established antioxidant properties, its role in maintaining epithelial integrity, and its influence on prostaglandin synthesis and glutathione (GSH) metabolism (Premkumar et al 2008a), vitamin B_2 (10 mg) has been trialled in combination with coenzyme Q10 (100 mg) and niacin (50 mg) (known as CORN) together with tamoxifen in breast cancer patients. The results of the studies have consistently demonstrated augmenting actions — enhanced manganese superoxide dismutase (MnSOD) expression, resulting in prevention of cancer cell proliferation (Premkumar et al 2008b), reduction of lipid peroxides (which are elevated in breast cancer and associated with tumour promotion) (Yuvaraj et al 2008), reduced tumour markers CEA and CA 15-3 and reduced serum cytokines (IL1 beta, IL6, IL8, TNFA & VEGF) (Premkumar et al 2008a). In addition to this, CORN supplementation reduced pro-angiogenic markers, with a corresponding increase in anti-angiogenic markers. Given that the growth and metastasising capacity of any tumour (but particularly of breast tumours) is dependent upon angiogenesis, this could represent a means to improved prognoses (Premkumar et al 2008a). Finally, CORN supplementation was shown to moderate some of the negative side effects of tamoxifen treatment, with normalisation of lipid and lipoproteins following 90 days of treatment in postmenopausal breast cancer patients (Yuvaraj et al 2007).

Role in folate and pyridoxine metabolism and the methylation pathologies

Effective one-carbon metabolism relies on nutrients beyond folate, B_6 and B_{12} — most notably B_2, which, although attracting significantly less research

attention, remains critical. Riboflavin, as FAD, is the cofactor for methylenetetrahydrofolate reductase (MTHFR), responsible for converting folate into its active form (Powers 2003, 2005, Sharp et al 2008). Consistent with this, there is emerging evidence of substantial interplay between folate and riboflavin in conditions previously associated only with folate deficiency or ameliorated by folate treatment. For example, plasma levels of vitamin B_2 and homocysteine have been shown to correlate (de Vogel et al 2008), especially in individuals with the MTHFR C677TT genotype (McNulty et al 2006). Preliminary studies employing combinations of folate (400 microgram) and riboflavin (5 mg) have demonstrated improved efficacy over folate alone, for example in colorectal cancer (Powers 2005). Additionally, high doses of folate alone have been reported to modestly but significantly reduce vitamin B_2 levels (Powers 2005). Taken together with the knowledge that riboflavin is central to pyridoxine metabolism (McCormick 2000), there is growing interest in the therapeutic potential of riboflavin in pathologies associated with poor methylation.

Sickle cell anaemia

Riboflavin supplementation (5 mg twice daily for 8 weeks) in patients with sickle cell anaemia resulted in improved haematological measurements compared with controls, suggesting that riboflavin enhances erythropoiesis (Ajayi et al 1993).

Rheumatoid arthritis

One study has suggested that patients with higher pain scores and active disease are at significantly greater risk of riboflavin deficiency than those with inactive disease (Mulherin et al 1996). In this study of 91 patients, pain score, articular index, C-reactive protein and erythrocyte sedimentation rate were all increased in those patients exhibiting riboflavin deficiency (all $P < 0.02$). It is unclear whether riboflavin deficiency influences pain threshold or is a result of the disease.

Other uses

Riboflavin is also used to treat carpal tunnel syndrome and acne, although only case reports are available (Folkers et al 1984).

DOSAGE RANGE

- Migraine prevention: 400 mg/day, taken for at least 3 months.
- Treating deficiency states: 10 mg/day.
- As an adjunct to tamoxifen in breast cancer treatment: 10 mg/day together with coenzyme Q10 100 mg/day and niacin 50 mg/day — based on preliminary evidence.

Australian RDI

<70 years
- Women: 1.1 mg/day.
- Men: 1.3 mg/day.

>70 years
- Women: 1.3 mg/day.
- Men: 1.6 mg/day.

Intake of vitamin B_2 causes a characteristic bright yellow-orange discolouration to urine.

TOXICITY

Riboflavin is considered an extremely safe supplement. Even at the high doses (400 mg) used in some of the trials, riboflavin remains non-toxic.

ADVERSE REACTIONS

General side effects noted in trials using high doses were reasonably uncommon, but included diarrhoea and polyuria (Bianchi et al 2004). One case of anaphylaxis has been reported (Ou et al 2001).

SIGNIFICANT INTERACTIONS

Certain medicines can increase the body's requirements for riboflavin.

Antibiotics

Antibiotic drugs can reduce endogenous production of B-group vitamins — increase intake of vitamin B_2.

Oral contraceptive pill

The OCP may increase demand for vitamin B_2 (Pelton et al 2000) — consider increasing intake with long-term use.

Tricyclic antidepressants

Reduces the absorption of riboflavin — may increase riboflavin requirements (Pelton et al 2000).

Amitryptyline

Increases the renal excretion of riboflavin (Bianchi et al 2004) — consider increased dietary intake with long-term use.

CONTRAINDICATIONS AND PRECAUTIONS

None known.

PREGNANCY USE

Considered safe.

PRACTICE POINTS/PATIENT COUNSELLING

- Vitamin B_2 deficiency signs include poor wound healing, hair loss, greasy dermatitis, ocular disturbances, failure to grow in children, angular stomatitis, cold sores, cracked lips and magenta tongue.
- Besides inadequate intake, deficiency can also result from chronic diarrhoea, liver disease and chronic alcoholism.
- There is some evidence suggesting that high-dose supplements (400 mg daily) significantly reduce the frequency of migraine headaches.
- Preliminary evidence suggests that regular supplementation with a multivitamin may also reduce the risk of developing cataracts.
- Supplementation results in a characteristic yellow-orange discolouration of urine.

PATIENTS' FAQs

What will this vitamin do for me?

Vitamin B_2 is essential for health and is involved in many different biochemical processes in the body. Research has suggested that when taken in high doses it can significantly reduce the incidence of migraine headaches.

When will it start to work?

Deficiency is reversed rapidly with supplementation. If using riboflavin to prevent migraine headaches, 3–4 months' treatment is required to see significant effects.

Are there any safety issues?

The vitamin is considered a safe nutrient.

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Vitamin B_3 — niacin

HISTORICAL NOTE The term 'niacin' is used interchangeably with nicotinic acid, and is also used collectively to include nicotinamide (or niacinamide), the amide form of nicotinic acid. Niacin originally derived its name from its discovery as an oxidation by-product of nicotine, and has been used generically since the 1940s to label foods and avoid association with nicotine, the alkaloid from tobacco. Nicotinic acid was the first hypolipidaemic agent shown to decrease the incidence of secondary myocardial infarction and reduce total mortality in these patients (Wilson et al 1991).

BACKGROUND AND RELEVANT PHARMACOKINETICS

Vitamin B_3 (niacin) is a water-soluble vitamin of the B complex family. Both nicotinic acid and nicotinamide are absorbed in the stomach and small intestine by passive diffusion at high doses, or by sodium-dependent facilitated diffusion at low doses, and excreted in the urine. Recent studies suggest that niacin uptake may be regulated by an acidic pH-dependent carrier-mediated system and protein-tyrosine-kinase (PTK)-mediated pathway (Nabokina et al 2005). The immediate-release form of nicotinic acid reaches peak concentration at 45 minutes and the extended release form in 4–5 hours. While nicotinamide can be directly converted to nicotinic acid, nicotinic acid must undergo a number of metabolic steps to produce nicotinamide adenine dinucleotide + (NAD+) before being converted to nicotinamide (Hendler & Rorvik 2001, Wilson et al 1991). The body's niacin requirement is also met by the biosynthesis of niacin from tryptophan, an amino acid. It has been estimated that each 60 mg excess of tryptophan (after protein synthesis) is converted to approximately 1 mg of niacin. In the absence of sufficient levels of vitamin B_3, the body will preferentially convert tryptophan to B_3. Niacin is widely distributed throughout the body and concentrates in the liver, spleen and adipose tissue. It is finally excreted by the kidneys.

Common forms available

The term niacin is used to refer to both nicotinic acid (niacin) and nicotinamide (niacinamide). Niacin is also referred to as vitamin B_3.

The immediate-release form, which requires more regular dosing, is associated with significant vasodilation ('flushing'), whereas the sustained-release form is associated with an increased risk of adverse events. Extended-release forms of niacin allow once-daily dosing and avoid much of the flushing and hepatotoxicity of the immediate- and sustained-release preparations (Sadovsky 2002).

FOOD SOURCES

Organ and muscle meats, lamb's liver, beef, poultry, fish, yeast, legumes, peanuts, Vegemite, yeast, wheat bran and fruit all contain vitamin B_3. Trace amounts are found in vegetables and eggs and, although milk contains only small amounts of B_3, it is a good source of tryptophan, which can be converted to B_3 in the body. In cereals such as corn and wheat it is present in a bound form, such as glycoside niacytin, which is unavailable to the body and has negligible nutritional value. Soaking corn in an alkaline solution such as lime helps to increase B_3 bioavailability.

Maximum loss in cooking is 75% (Wahlqvist 2002).

DEFICIENCY SIGNS AND SYMPTOMS

Pellagra is a deficiency syndrome of vitamin B_3, due to inadequate conversion of tryptophan to niacin or a lack of dietary niacin or tryptophan. The main symptoms are often referred to as 'the four Ds' (Jacobs & Wood 2003):

- diarrhoea
- dermatitis — primarily on sun-exposed areas such as the face, hands, feet and arms. The rash starts as red, itchy areas that develop vesicles, blisters, scales and fissures. At the final stage, the skin becomes thickened, lichenified and hyperpigmented (Hendler & Rorvik 2001).
- dementia — may include aggressiveness and cloudy thinking (Llancapi et al 1998)
- death — if left untreated, vitamin B_3 deficiency can be fatal.

Vitamin B_3 deficiency may be found in conjunction with other deficiencies and may be associated with peripheral neuropathy. Early signs include anorexia, weakness, anaemia, glossitis, redness on sun-exposed areas and photosensitivity. Inadequate niacin status (niacin ratio ≤ 1) has been reported in 26.7% of older adults (Paulionis et al 2005).

Primary deficiency

This usually occurs in areas where maize (Indian corn) forms a major part of the diet. Bound niacin, found in maize, is not assimilated in the intestinal tract unless it has been previously treated with alkali, as in the preparation of tortillas. Corn protein is also deficient in tryptophan. Amino acid imbalance may also contribute to deficiency, since pellagra is common in India among people who eat millet with a high leucine content.

In Western industrialised countries such as Australia, New Zealand and USA, vitamin B_3 deficiency is mostly associated with conditions that affect the person's nutritional intake such as alcoholism, mental illness or homelessness. It may also occur in anorexia nervosa, where dietary niacin and tryptophan are deficient (Prousky 2003).

Secondary deficiency

This may develop in conditions associated with diarrhoea, cirrhosis or malabsorption, as well as after extensive postoperative use of parenteral nutrition lacking adequate niacin. Pellagra may occur during prolonged isoniazid therapy (the drug replaces nicotinamide in NAD), in malignant carcinoid tumour (tryptophan is diverted to form 5-hydroxytryptamine), and in Hartnup disease, an autosomal recessive disorder in which there is defective conversion of tryptophan to niacin (Beers & Berkow 2003). It has also been observed in Crohn's disease, most likely due to malnutrition and intestinal malabsorption (Abu-Qurshin et al 1997).

MAIN ACTIONS

Vitamin B_3 is involved in a wide range of biological functions, such as energy production, fatty acid synthesis, cholesterol and steroid synthesis, signal transduction, regulation of gene expression and maintenance of genome integrity. Other functions of vitamin B_3 include the regulation of blood sugar, antioxidant mechanisms and detoxification reactions (IMG 2006).

Niacin is a dietary precursor for the coenzymes NAD+ and nicotinamide adenine dinucleotide phosphate (NADP), which are involved in a number of metabolic functions such as DNA synthesis (Hageman & Stierum 2001), glycolysis, fatty acid

synthesis and cellular respiration (Kobayashi & Shimizu 1999). NAD+ exerts potent effects through a number of enzymes that alter protein function, regulate apoptosis, DNA repair, stress resistance, metabolism and endocrine signalling (Sauve 2008). NADH, the reduced form of beta-nicotinamide adenine dinucleotide, is also synthesised from niacin (B_3) and is required to supply protons for oxidative phosphorylation (Depeint et al 2006). Like chromium, vitamin B_3 is an important component of glucose tolerance factor. Niacin can also be preferentially converted from tryptophan, and as a result a deficiency of niacin can impact on other functions of tryptophan, such as neurotransmitter production.

Lipid-lowering

Large doses of niacin (nicotinic acid) reduce total cholesterol, LDL-cholesterol, triglycerides and lipoprotein(a) levels and also markedly raise HDL-cholesterol levels (Illingworth et al 1994). In human trials extended-release niacin (2 g/day) lowers plasma TG levels and raises plasma HDL, increases apolipoprotein A-I concentrations and production, as well as enhancing clearance of TG-rich lipoproteins apoB-100 and apoB-48 (Lamon-Fava et al 2008). The beneficial effects of niacin in reducing triglycerides and lipoproteins that contain apolipoprotein-B (such as VLDL and LDL) are thought to be mediated by inhibiting fatty acid mobilisation from adipose tissue triglyceride stores and increasing intracellular apolipoprotein-B degradation, resulting in decreased secretion of VLDL and LDL particles (Ganji et al 2003). The cardioprotective properties of HDL-cholesterol appear to be due to its involvement in processes such as reverse cholesterol transport and inhibition of LDL-cholesterol oxidation (Ganji et al 2003, Kwiterovich 2000).

Anti-atherogenic

In addition to its lipid-lowering ability, preliminary studies suggest that niacin inhibits vascular inflammation by decreasing endothelial reactive oxygen species (ROS) production and subsequent LDL oxidation and inflammatory cytokine production, key events in the atherogenic process (Ganji et al 2009).

Impairs glucose regulation

Although niacin is an important part of glucose tolerance factor, in high doses it may impair glucose regulation, resulting in insulin resistance, increased insulin secretion and increased fasting blood glucose in patients with type 2 diabetes, although some authors suggest that niacin is both safe and effective in diabetes (Meyers et al 2004).

Interestingly, nicotinamide has also been shown to cause insulin resistance, resulting in increased insulin secretion in healthy subjects with a family history of type 1 diabetes (Greenbaum et al 1996).

Modest increases in fasting blood glucose levels have been noted in a number of clinical trials (Elam et al 2000, Goldberg 1998, Rindone & Achacoso 1996), although other trials have found that changes in fasting blood glucose reverted to normal at 4 months (Grundy et al 2002) and 8 months (Zhao et al 2004).

In practice, this effect on glucose regulation may not be clinically significant (Gardner et al 1997, Guyton 2004, Meyers et al 2004, Zhao et al 2004) and the potential benefits of improved lipid control in diabetic patients for whom other lipid-lowering medications provide inadequate control may outweigh any concerns. Nevertheless hypoglycaemic medications may need to be monitored and adjusted if necessary (Fonseca 2003).

Antioxidant

Niacinamide has been shown in vitro to have an antioxidant activity comparable to that of ascorbic acid (Hageman & Stierum 2001).

Protects beta-cells in the pancreas

Nicotinamide has been shown to protect beta cells from inflammatory insults and to improve residual beta-cell function in patients after onset of type 1 diabetes (Lampeter et al 1998). It may also prevent damage to beta cells by the immune system as a result of its antioxidant effects (Anderson 1994).

Chondroprotection

The generation of IL-1 in the synovium and subsequent induction of nitric oxide (NO) synthase is crucial to the pathogenesis of osteoarthritis. The ability of niacinamide to suppress cytokine-mediated induction of NO synthase in a number of types of cells (McCarty & Russell 1999) provides a theoretical basis for its use as a chondroprotective agent.

Chemoprotection

The dietary status of niacin has the potential to affect DNA repair, genomic stability and the immune system, thus influencing cancer risk (Kirkland 2003), and increased demand may occur in many malignancies, including primary hepatoma (Jacobs & Wood 2003).

In vitro studies have shown that NAD+ is important for activity of PARP-1, an enzyme that is thought to be important for genomic stability. In vitro and animal studies have indicated that niacin deficiency increases genomic instability and may increase the risk of certain tumours. While NAD+ is niacin dependent, high doses of nicotinamide inhibit PARP-1 in vitro; hence, the effects may be dose dependent (Hageman & Stierum 2001). Niacin as a precursor for NAD+ also inhibits DNA strand breakage in vitro and stimulates repair (Weitberg & Corvese 1990).

Neuroprotective

In experimental models of Parkinson's disease, high doses of nicotinamide, a precursor for the coenzyme beta-nicotinamide adenine dinucleotide (NAD+), decreased oxidative stress and improved mitochondrial and motor function (Jia et al 2008). It has also been shown to preserve both neuronal and vascular cell populations in brain injury, and affect both intrinsic cellular integrity and extrinsic

cellular inflammation suggesting potential use in neurodegenerative diseases (Li et al 2004).

CLINICAL USE

Deficiency

Severe deficiencies of niacin and tryptophan, a precursor from which the body can synthesise niacin, are the principal causes of pellagra.

Anorexia nervosa

The most common features of pellagra in patients with anorexia nervosa include erythema on sun-exposed areas, glossitis and stomatitis. A trial of supplementation with 150–500 mg for 24–48 hours will quickly determine if symptoms are due to pellagra (Prousky 2003).

HIV and tryptophan depletion

A pellagra-like state can develop in malnourished patients with HIV and this may be due to impaired niacin status (Monteiro et al 2004) and result in tryptophan depletion. As tryptophan is preferentially converted to vitamin B_3 (if B_3 is depleted), a trial was conducted using high-dose niacin for 2 months in HIV patients and it was found that the high-dose niacin increased plasma tryptophan levels by 40% (Murray et al 2001).

An open, prospective trial has also concluded that extended-release niacin therapy is safe and effective for the treatment of dyslipidaemia associated with antiretroviral therapy; 2000 mg/day was given to 14 subjects for 14 weeks and resulted in significant reductions in serum levels of triglycerides, total cholesterol and non-HDL cholesterol (Gerber et al 2004).

Depression

As tryptophan is a precursor to serotonin, the preferential conversion of tryptophan to B_3 in deficiency states may theoretically result in serotonin depletion. If sufficiently severe, this could produce symptoms of depression.

Hypercholesterolaemia and hypertriglyceridaemia

Niacin has been widely used since the 1950s as a pharmacological agent to regulate abnormalities in plasma lipid and lipoprotein metabolism and in the treatment of atherosclerotic cardiovascular disease (Ganji et al 2003). Large doses of niacin reduce total cholesterol, LDL cholesterol, triglycerides and lipoprotein(a) levels, and also markedly raise HDL cholesterol levels (Illingworth et al 1994). According to a recent meta-analysis, effects on LDL cholesterol and triglycerides appear to be more significant in females, especially at doses of >1500 mg/day (Goldberg 2004).

Extended-release niacin (nicotinic acid) has been evaluated in at least four randomised, placebo-controlled trials, with the most efficacious results occurring at doses of 1500–2000 mg/day (Goldberg 1998, Grundy 2002, Guyton et al 2000, Morgan et al 2003). Results were dose- and time-dependent, with trials ranging in length from 4 to 16 weeks. At the 1500 and 2000 mg doses, reductions were noted in total cholesterol (–7 to –12.1%); total cholesterol to HDL cholesterol ratio (–17 to –22%); LDL cholesterol (0 to –7%); triglycerides (–16 to –36%); and lipoprotein(a) (–7 to –23.6%). One trial noted a particular decrease in the smaller, more atherogenic, dense LDL particles and an increase in the larger, cardioprotective HDL particles (Morgan et al 2003). HDL cholesterol increased by 21–25.8% and apolipoprotein A-I levels were reported in one study to have increased 9–11% (Guyton et al 2000). The main side effects reported were flushing, a 5% increase in fasting blood glucose, pruritis and rash (Goldberg 1998).

While existing guidelines for the prevention and treatment of coronary artery disease tend to focus on reducing LDL cholesterol, there is growing evidence linking low HDL cholesterol levels with an increased risk of atherosclerosis. As niacin significantly increases HDL cholesterol, and may also improve total cholesterol, LDL cholesterol and triglyceride levels, as well as exhibiting antioxidant,

Clinical note — Major lipids affecting cardiovascular disease risk

Cardiovascular risk is predicted by a number of factors; however, the major lipids involved are LDL cholesterol lipoprotein(a), triglycerides and HDL cholesterol. Furthermore, LDL particle size and number are associated with different levels of atherogenicity.

A reduction in HDL cholesterol and an increase in triglycerides and LDL cholesterol has been associated with an increased risk of cardiovascular disease. On the other hand, high HDL cholesterol is protective against atherosclerosis and is inversely related to risk of early coronary heart disease (Packard et al 2002). Its cardioprotective properties appear to be due to its involvement in processes such as reverse cholesterol transport and inhibition of LDL-cholesterol oxidation (Kwiterovich 2000). It has been suggested that niacin has the potential to regress atherosclerosis because of its ability to affect reverse cholesterol transport out of vessel walls (Rubic et al 2004).

Furthermore, the LDL phenotype B, characterised by small, dense LDL particles, is associated with increased atherogenicity compared to phenotype A, and niacin increases LDL particle size from small LDL to the less atherogenic, large LDL subclasses (Morgan et al 2004). The frequency of the LDL phenotype B increases as HDL's decrease and triglycerides increase.

Lipoprotein(a) has been identified as an independent risk factor for premature coronary artery disease and aggravates the atherogenic effect of diabetes mellitus (Wassef 1999).

A 2002 review highlights the ability of niacin to effectively lower triglycerides, raise HDL cholesterol and shift LDL particles to the less atherogenic phenotype A — all important factors that reduce the risk of cardiovascular disease (Ito 2002).

anti-inflammatory and other benefits, it is a prime candidate for the prevention and treatment of atherosclerosis (Sanyal et al 2007). A 2002 review suggests that niacin is the 'only agent currently available that favourably affects all components of the lipid profile to a significant degree' and has the greatest effect on HDL levels (Pieper 2002). In a double-blind RCT, 107 patients with coronary artery disease received 1000 mg/day extended-release niacin (ER-niacin) or a placebo for 12 weeks. ER-niacin improved endothelial dysfunction, triglycerides ($P = 0.013$), LDL cholesterol ($P = 0.013$) and HDL cholesterol ($P < 0.0001$). However, best results were seen in patients with low baseline HDL cholesterol (Warnholtz et al 2009).

Niacin may also be combined with chromium (Bolkent et al 2004, Shara et al 2005, Yanardag et al 2005) or phytosterols (Yeganeh et al 2005) for synergistic effects.

Combined therapy: statins and niacin

Although monotherapy with statin drugs (HMG-CoA reductase inhibitors) causes significant reductions in LDL cholesterol, they provide only modest improvements in triglycerides and HDL cholesterol. Niacin, on the other hand, provides significant reduction of triglycerides and enhancement of HDL cholesterol levels, although reductions in LDL cholesterol are less significant. As a result, combinations of these lipid-modifying agents will better address lipid abnormalities and improve clinical outcomes (Ito 2002, Levy & Pearson 2005).

In practice, the concurrent use of niacin with a statin has demonstrated improved outcomes in patients for whom monotherapy was unable to achieve adequate lipid control (Gardner et al 1997, Guyton & Capuzzi 1998). The combination may also slow the progression of atherosclerosis in individuals with known coronary heart disease and moderately low HDL-cholesterol (Taylor et al 2004).

Numerous studies exist to support the safe and effective use of extended-release niacin with lovastatin (Armstrong et al 2004, Bays et al 2003, Rubenfire 2004), simvastatin (Kaur et al 2004, Zhao et al 2004), pravastatin (Gardner et al 1997), and rosuvastatin (Capuzzi et al 2003).

In a 24-week trial of 319 high-risk patients with predominantly mixed dyslipidaemia who received simvastatin alone (20 mg/day) or a combination of simvastatin (20 mg/day) plus extended release niacin (1000 or 2000 mg/day), there was a significant dose-dependent decrease in non-HDL cholesterol (–13.9% and –22.5% versus –7.4%; $P < 0.01$). Significant improvements in HDL cholesterol, triglycerides, apolipoprotein B, lipoprotein(a) and total to HDL cholesterol ratio were also observed. Niacin treatment was generally well tolerated, with □ 60% of patients reporting flushing (> 90% of whom described the flushing as mild or moderate in intensity) and only 7.5% discontinuing due to the flushing (Ballantyne et al 2008). The OCEANS study (**O**pen-label evaluation of the safety and efficacy of a **C**ombination of niacin **E**R and simv**A**statin in patie**N**ts with dy**S**lipidaemia) also evaluated the safety and efficacy of a combination of extended release niacin (2000 mg/day) and simvastatin (40 mg/day) over 52 weeks in 520 patients with mixed dyslipidaemia. At 24 weeks, improvements in non-HDL cholesterol (–27.3%), LDL cholesterol (–25.0%), HDL cholesterol (+23.9%), and triglycerides (–35.9%) (all $P < 0.0001$ vs baseline) were reported. Once again the treatment was generally well tolerated: 71% of patients experienced flushing, of whom 92% were rated as mild or moderate in intensity. In those who experienced flushing, the effects decreased over time, with < 40% reporting flushing during the final 12 weeks of the trial and only 7% discontinuing the trial because of flushing. The combination appears to be both effective and well tolerated in achieving therapeutic lipid goals (Karas et al 2008).

Lovastatin plus extended-release niacin have also been investigated and found to be comparable to atorvastatin and more effective than simvastatin in reducing LDL cholesterol, more effective in increasing HDL cholesterol and to provide greater global improvements in non-HDL cholesterol, triglycerides, and lipoprotein(a) (Bays et al 2003). The combination is associated with good compliance and safety (Rubenfire 2004) and may also be less costly than simvastatin (Armstrong et al 2004).

In a clinical trial of diabetic patients, the addition of niacin 500 mg three times daily to pravastatin 20 mg resulted in a significant lowering of LDL cholesterol compared with pravastatin monotherapy. Furthermore, improvements in lipid profile were gained without compromising glycaemic control (Gardner et al 1997). In a separate trial of simvastatin plus niacin among people with diabetes, glycaemic control initially declined mildly but returned to pretreatment levels at 8 months and remained stable for the remainder of the study (Zhao et al 2004).

As early studies indicated a potential for myopathy, rhabdomyolysis and hepatotoxicity, use of the sustained-release form of niacin in combination with statins is controversial. Although current trials tend to focus on the safer extended-release form, liver function should be monitored and patients observed for symptoms of myopathy (Guyton & Capuzzi 1998).

Low-dose niacin therapy (50 mg twice daily) in combination with statins for 3 months may also significantly increase HDL cholesterol, while avoiding the side effects commonly associated with higher doses (Wink et al 2002).

Diabetes

In people with diabetes, the extended-release niacin may be useful in treating diabetic dyslipidaemia (Pan et al 2002); however, research has indicated the possibility of impaired glucose regulation in patients with type 2 diabetes. In practice this may not be clinically significant (Gardner et al 1997, Guyton 2004, Meyers et al 2004, Zhao et al 2004), and the potential benefits of improved lipid control in diabetic patients for whom other lipid-lowering medications provide inadequate control may outweigh any concerns. Nevertheless, hypoglycaemic medications may need to be monitored and adjusted if necessary (Fonseca 2003).

OTHER USES

Metabolic syndrome

Metabolic syndrome, also known as syndrome X or insulin-resistance syndrome, is a highly prevalent condition that significantly increases the risk of coronary heart disease and is associated with elevated triglycerides, low HDL cholesterol and LDL cholesterol. As niacin raises HDL cholesterol, lowers triglycerides and increases LDL cholesterol particle size, it may be considered a useful therapeutic option for the treatment of dyslipidaemia in such cases (Ito 2004). The potential for niacin to negatively affect glucose metabolism and insulin resistance has led to concerns about its use in practice; however, a recent 3-year trial using niacin plus simvastatin suggests that as long as careful attention is paid to glycaemic control the benefits of niacin appear to outweigh the deleterious effects (Vittone et al 2007).

Preventing diabetes

Nicotinamide has been proposed as a useful therapeutic agent for the prevention of type 1 diabetes and also as an adjunct to intensive insulin therapy (Pocoit et al 1996). Interestingly, nicotinamide has also been shown to cause insulin resistance, resulting in increased insulin secretion in healthy subjects with a family history of type 1 diabetes (Greenbaum et al 1996). A concern therefore exists that monitoring such people for signs of development of the disease may be complicated by the use of nicotinamide.

Protects beta cells

Type 1 diabetes is characterised by progressive beta cell destruction, which leads to complete insulin deficiency; at the time of diagnosis, 80–90% of beta cells have been destroyed (Virtanen & Aro 1994). Nicotinamide has been shown to protect beta cells from inflammatory insults and to improve residual beta-cell function in patients after onset of type 1 diabetes (Gale 1996, Lampeter et al 1998).

One RCT using 25 mg/kg versus 50 mg/kg nicotinamide in early-onset type 1 diabetes (< 4 weeks) found that both doses were likely to be effective in reducing beta-cell dysfunction. As a higher dose may cause insulin resistance, the lower dose is probably preferable (Visalli et al 1999).

Alternatively, another RCT that used slow-release nicotinamide failed to detect a reduction in diabetes incidence after 3 years (Lampeter et al 1998).

Osteoarthritis

As the generation of IL-1 in the synovium and subsequent induction of nitric oxide (NO) synthase is crucial to the pathogenesis of osteoarthritis, the ability of niacinamide to suppress cytokine-mediated induction of NO synthase in a number of types of cells (McCarty & Russell 1999) provides a theoretical basis for its use in the prevention of this condition.

Positive results obtained by a randomised, double-blind, placebo-controlled trial support this theory. In the study, 72 patients with osteoarthritis were treated over 12 weeks with niacinamide or a placebo; active treatment improved the global impact of osteoarthritis, enhancing joint flexibility, reducing inflammation and allowing for reduction in standard anti-inflammatory medications (Jonas et al 1996).

Cancer prevention

Because niacin is required for genomic stability and a deficiency is associated with an increased risk of certain tumours, it has been suggested that niacin may reduce the risk of various cancers (Hageman & Stierum 2001).

Migraine

A systematic review concluded that niacin may have beneficial effects on migraine and tension-type headaches (Prousky & Seely 2005). The effects may be mediated by vasodilation, improved mitochondrial energy metabolism or the correction of low plasma levels of serotonin, which have been implicated in migraine pathogenesis. Niacin may act as a negative feedback regulator to shunt tryptophan into the serotonin pathway, thus increasing plasma serotonin levels (Velling et al 2003).

Alzheimer's dementia

Dementia can be caused by severe niacin deficiency and a prospective study of 6158 people aged > 65 years found that dietary niacin intake (as determined by a food-frequency questionnaire) had a protective effect on the development of Alzheimer's dementia and cognitive decline (Morris et al 2004).

Other conditions

Experimental and clinical studies have suggested that niacin and nicotinamide have potential benefits in reducing hyperphosphataemia in dialysis patients; however, further rigorous trials are required to confirm safety and efficacy (Berns 2008). Although substantial evidence is so far lacking, niacin has also been proposed as a treatment for

Clinical note — Patients with schizophrenia rarely experience skin-flushing side effect

The relative absence of skin flushing in response to niacin supplementation by patients with schizophrenia (80% versus 20%) has been attributed to a reduced pharmacological sensitivity rather than an inadequate cutaneous vasodilatory response. As the skin flush response is prostaglandin-mediated, schizophrenia may be associated with essential fatty acid deficiency or abnormalities in enzymes, receptors or signal transduction mechanisms that affect the synthesis, release or response to vasodilatory PG (Messamore 2003, Messamore et al 2003, Tavares et al 2003). The diminished response is more evident with increasing age, male gender and in the early stages of the disease (Smesny et al 2004, 2005). Diminished sensitivity to niacin skin tests in early psychosis may predict the severity of symptoms (Smesny et al 2003, 2005).

Clinical note — Differences between major forms of niacin supplements

Three main forms of niacin supplements are produced, each with their own set of safety issues. Immediate-release niacin is associated with increased incidence of flushing and other adverse reactions, whereas sustained-release forms have been associated with potential liver damage (Henkin et al 1990, McKenney 2004). In comparison, extended-release niacin has been found to have similar efficacy to immediate-release forms but results in minimal flushing, myopathy or hepatotoxicity (Guyton 2004, McKenney 2004, Pieper 2002, Yim & Chong 2003). Current evidence suggests that the extended-release formulation of niacin has a significantly better safety profile than other niacin formulations and compares favourably with other commonly used lipid-lowering medications. The safety of combined statin and extended-release niacin (niacin-ER) is comparable with the safety of each of the drugs alone (Alsheikh-Ali & Karas 2008).

No-flush preparations of OTC niacin contain no free nicotinic acid and are unlikely to be effective in treating dyslipidaemia (Meyers et al 2003).

psoriasis (Tang et al 2008), intermittent claudication, Raynaud's syndrome and hypothyroidism.

DOSAGE RANGE

Australian RDI

- Women: 11 mg/day.
- Men: 12 mg/day.

Administration with food maximises bioavailability and minimises GI intolerance.

High blood cholesterol and triglyceride levels

- 1500–2000 mg pure crystalline niacin (nicotinic acid) daily — this level should be reached gradually over a period of 4–6 weeks.
- 1500–2000 mg taken once daily for extended-release preparations (best taken at night).
- Inositol hexaniacinate is often associated with less flushing (Rakel 2003).

ADVERSE REACTIONS

Flushing is a common side effect of niacin therapy and may lead to discontinuation of therapy in some individuals (Rubenfire 2004). Night-time administration of extended-release niacin appears to reduce this effect, as does concurrent administration of aspirin (Mills et al 2003, White Robinson et al 2000).

Niacin has been associated with palpitations, worsening of diabetes control, exacerbation of peptic ulcer disease, gout, hepatitis (Crouse 1996), chills, generalised pruritus, gastrointestinal upset, and cutaneous tingling (Mills et al 2003). A case report also exists of increased intraocular pressure in a 73-year-old man with a history of primary open-angle glaucoma taking 500 mg of oral niacin; each time the niacin was withdrawn, the intraocular pressure returned to original levels (Tittler et al 2008).

Reports of hepatotoxicity resulting from sustained-release niacin supplementation appear to be idiosyncratic, as there is no evidence to suggest intrinsic hepatotoxic activity; this also appears to be the case for statins (Parra & Reddy 2003).

SIGNIFICANT INTERACTIONS

Antiretroviral therapy

Extended-release niacin may improve the dyslipidaemia associated with antiretroviral therapy and is considered a safe and effective therapeutic option (Gerber et al 2004). Beneficial interaction is possible.

Diabetes medications

Niacin may affect glycaemic control and increase fasting blood-glucose levels. Therefore medication doses may need to be reviewed: exercise caution and monitor drug requirements when prescribing diabetes medications concurrently with niacin.

Hypolipidaemic agents

Several clinical studies confirm the lipid-lowering effects of vitamin B_3. Although a beneficial interaction has been shown in clinical trials with statin drugs, similar additive effects are theoretically possible with other hypolipidaemic drugs. Beneficial interaction is possible.

Imipramine

A combination of imipramine with L-tryptophan 6 g/day and niacinamide 1500 mg/day has been shown to be more effective for people with bipolar disorder than imipramine alone (Chouinard et al 1979). Beneficial interaction possible.

Isoniazid

Prolonged isoniazid therapy (the drug replaces niacinamide in NAD) may induce pellagra (Beers & Berkow 2003). Increased vitamin B_3 intake may be required with long-term therapy. Beneficial interaction is possible.

Oral contraceptive pill

Use of the oral contraceptive pill may reduce vitamin B_3 levels (Lininger 1999). Increased vitamin B_3 intake may be required with long-term therapy. Beneficial interaction is possible.

Statin drugs (HMG-CoA reductase inhibitors)

The combined use of niacin and statins, including atorvastatin (Lipitor), fluvastatin (Lescol), lovastatin (Mevacor), pravastatin (Pravachol) and simvastatin (Zocor), has been found to provide added therapeutic effects and reduce requirements for statin medications (Ballantyne et al 2008, Karas et al 2008, Gardner et al 1996, 1997, Jacobson et al 1994, Yim & Chong 2003). The addition of niacin may enhance or improve the lipid profile of those who require a further decrease of triglycerides and/or LDL cholesterol and/or increase of HDL cholesterol, even after stable statin therapy.

It should be noted that drug label warnings of an increased risk of adverse events with combined

statin and niacin therapy have been based solely on case reports and are not supported by the scientific literature (Alsheikh-Ali & Karas 2007). Beneficial interaction is possible.

As early studies using the sustained-release form of niacin in combination with lovastatin indicated a potential for myopathy, rhabdomyolysis and hepatotoxicity, use of this form is controversial. Liver function should be monitored and patients observed for symptoms of myopathy (Guyton & Capuzzi 1998). Use sustained-release niacin with caution.

Tamoxifen

The addition of niacin, riboflavin and coenzyme Q10 to tamoxifen therapy may improve mitochondrial antioxidant status and antitumour activity (Perumal et al 2005). The exact role of niacin is unclear; however, the addition of antioxidants to tamoxifen therapy may prove advantageous. Beneficial interaction is possible.

CONTRAINDICATIONS AND PRECAUTIONS

Supplemental vitamin B_3 should be used with caution in conditions involving insulin resistance, although the potential benefits may outweigh the slight increase in blood glucose. In such cases, medication requirements may need to be revised.

As early studies indicated a potential for myopathy, rhabdomyolysis and hepatotoxicity, use of the sustained-release form of niacin in combination with statins is controversial. Liver function should be monitored and patients observed for symptoms of myopathy (Guyton & Capuzzi 1998).

Gout

Excess supplementation can lead to increased production or crystallisation of uric acid (Rakel 2003).

Glaucoma

A case report exists of increased intraocular pressure in a 73-year-old man with a history of primary open-angle glaucoma taking 500 mg of oral niacin; each time the niacin was withdrawn, the intraocular pressure returned to original levels (Tittler et al 2008). Intraocular pressure should be monitored in patients at risk of glaucoma while taking niacin.

Drug screening

Severe adverse reactions (including hepatotoxicity, profound neutrophilia, QT(C)-interval prolongation, metabolic acidosis, nausea, vomiting, dizziness, skin reactions and hypoglycaemia evolving into hyperglycaemia) have been reported in people using high doses of niacin in the misguided belief that it will increase drug clearance and interfere with urine drug screening. Healthcare providers and drug screeners need to be alert to these potentially serious effects (Mittal et al 2007).

PREGNANCY USE

Nicotinic acid is classified as a category B2 medicine in pregnancy by the Australian Drug Evaluation Committee. This means that it has been taken by a limited number of pregnant women and women of childbearing age without any increase in malformations or other direct or indirect harmful effects on the human fetus having been observed.

PRACTICE POINTS/PATIENT COUNSELLING

- The term niacin is used interchangeably with nicotinic acid, and is also used collectively to include nicotinamide (or niacinamide), the amide form of nicotinic acid.
- In practice, nicotinic acid decreases the incidence of secondary myocardial infarction and reduces total mortality incidence in these patients.
- Large doses of niacin reduce total cholesterol, LDL cholesterol, triglycerides and lipoprotein(a) levels, and also markedly raise HDL cholesterol levels.
- The extended-release form appears to have a better safety profile, with reduced incidence of flushing.
- In high doses, it can impair glucose regulation, resulting in insulin resistance, increased insulin secretion and increased fasting blood glucose in patients with type 2 diabetes; care is therefore advised when using the supplement in this group of patients. Alternatively, nicotinamide protects beta cells from inflator damage and may improve residual beta-cell function in patients after onset of type 1 diabetes.

PATIENTS' FAQs

What will this vitamin do for me?

Niacin in high doses will favourably alter lipid levels and reduce the risk of cardiovascular disease, risk of heart attack and risk of death after heart attack. It may also be useful in diabetes when administered under professional supervision.

When will it start to work?

Beneficial effects on lipid levels have been seen within 4 weeks; however, several months of use may be required for optimal effects.

Are there any safety issues?

Several different forms of niacin supplements are produced; however, the extended-release form appears to have a better safety profile than the others and a reduced risk of flushing.

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Vitamin B_5 — pantothenic acid

BACKGROUND AND RELEVANT PHARMACOKINETICS

The Greek word *pantos* means 'everywhere'. As the name pantothenic acid implies, it is widely distributed and present in nearly all plant and animal foods. Sensitive to heat and both acid and alkali, considerable amounts are lost through the milling of cereal grains. The intestine is exposed to two sources of pantothenic acid: dietary and bacterial. Current research suggests that bacterial synthesis may be more dominant and important in ruminant species (Bates 1998). Approximately 50% of pantothenic acid is absorbed in the jejunum, an amount that decreases when doses 10-fold greater than the RDI are taken (Groff & Gropper 2009).

The organ with the highest concentration of pantothenic acid is the liver, followed by the adrenal cortex, which reflects the large requirements of these tissues and is indicative of the biochemical role of the vitamin's coenzyme derivatives. There are contrasting opinions about whether a genuine storage capacity exists for this vitamin; however, if there is any at all, the consensus is that pantothenic acid is 'stored' in very limited amounts and in those tissues with the greatest requirements (Groff & Gropper 2009).

Study of placental tissue demonstrates that biotin uses the same transport mechanisms as pantothenic acid, which may indicate competition between these two nutrients in other tissues (Bates 1998).

CHEMICAL COMPONENTS

Pantothenic acid is an amide and consists of B-alanine and pantoic acid joined by a peptide bond. In supplements, it is often found as calcium pantothenate.

FOOD SOURCES

The most concentrated sources are meats (especially liver), egg yolk, broad beans and legumes, but it is also found in many other foods such as whole grains, milk, peanuts, broccoli, avocado, mushroom and apricots. Up to 50% can be lost through cooking (Wahlqvist et al 2002).

Approximately 85% occurs in food as a component of coenzyme A (CoA), which is hydrolysed to pantothenic acid or pantethine during digestion.

DEFICIENCY SIGNS AND SYMPTOMS

Because pantothenic acid deficiency is so rare, most information regarding its signs and symptoms comes from experimental research in animals or cases of severe malnutrition. The deficiency picture appears to be generalised and species-specific (Bates 1998). Preliminary studies in humans using competitive analogues of pantothenic acid have produced the following symptoms:

- 'burning feet syndrome': this affects the lower legs and is characterised by sensation of heat
- cardiac instability
- gastrointestinal disturbance
- dizziness, paraesthesia and depression
- loss of immune (antibody) function
- insensitivity to adrenocorticotrophic hormone
- increased sensitivity to insulin
- vomiting
- fatigue
- weakness.

Some conditions that have been associated with increased requirements are:

- alcoholism (due to typically low intakes of vitamin B complex)
- diabetes mellitus (as a result of increased excretion)
- inflammatory bowel diseases (due to decreased vitamin absorption).

MAIN ACTIONS

Pantothenic acid is involved in myriad important chemical reactions in the body as a result of its involvement in CoA synthesis.

Coenzyme function

CoA and the krebs cycle

Pantothenic acid is required for CoA synthesis and cellular respiration, and plays a pivotal role in the oxidation of fatty acids and acetylation of other molecules, so as to enable transportation. Together with thiamine, riboflavin and niacin, it is involved in the oxidative decarboxylation of pyruvate and alpha-ketoglutarate in the Krebs cycle and ultimately is important for energy storage as well as release.

Acyl carrier protein

Pantothenic acid is the prosthetic group for acyl carrier protein and therefore is involved in the synthesis of fatty acids.

Indirect antioxidant effects

New in vitro research supports an indirect antioxidant role for pantothenic acid through its ability to increase cellular adenosine triphosphate (ATP), which in turn creates increased levels of free glutathione and enhanced protection of cells against peroxidative damage (Slyshenkov et al 2004).

Other functions

It is involved in the synthesis of amino acids, sterols (e.g. cholesterol) and vitamin D. It is necessary for production of the neurotransmitter acetylcholine and the formation of red cells. Vitamin B_5 plays an important role in adrenal function and, as CoA, is needed for proper adrenal cortex function and the synthesis of steroid hormones.

Lipid-lowering

Pantethine, a metabolite of pantothenic acid, has been investigated in several clinical studies and found to exert significant lipid-lowering activity (Coronel et al 1991, Donati et al 1986, Gaddi et al 1984).

The mechanism of action relates to reduced insulin resistance and activation of lipolysis in serum and adipose tissue, according to in vivo research (Naruta & Buko 2001). Additionally, inhibition of HMG-CoA reductase, as well as more distal enzymes in the cholesterol synthetic pathway, are likely to be responsible (McCarty 2001). More recently, an in vitro study demonstrated that pantethine produced a 50% inhibition of fatty acid synthesis and an 80% inhibition of cholesterol synthesis (McRae 2005).

Wound healing

Both oral and topical administration have been shown to accelerate closure of wounds and increase strength of scar tissue in vivo (Plesofsky 2002, Vaxman et al 1990). Both in vitro and in vivo studies reveal that topical dexpanthenol induces activation of fibroblast proliferation, which contributes to accelerated re-epithelialisation in wound healing (Ebner et al 2002).

CLINICAL USE

Although pantothenic acid has been investigated in some studies, most investigation has occurred with several of its derivatives, chiefly an alcoholic analogue of pantothenic acid called dexpanthenol (Bepanthen, see below) and pantethine.

Deficiency states: prevention and treatment

Traditionally, pantothenic acid is recommended together with other vitamin B complex nutrients to treat general deficiency or prevent deficiency in conditions such as alcoholism, diabetes mellitus and malabsorption syndromes.

Enhances wound healing

Pantothenic acid has been both used as an oral supplement and applied topically in a cream base to enhance wound healing; it has been shown to accelerate closure of wounds and increase strength of scar tissue in experimental animals (Plesofsky 2002, Vaxman et al 1990). Although these results are encouraging, there has been little investigation in humans. One double-blind study testing the effects of vitamin C (1000 mg) and pantothenic acid (200 mg) supplements over a 21-day period showed no significant alteration to wound healing with this treatment regimen (Vaxman et al 1995).

Topical use

Bepanthen is a well-known dermatological preparation containing dexpanthenol, an alcoholic analogue of pantothenic acid. It has been investigated in numerous studies and found to act like a moisturiser, activate fibroblast proliferation, accelerate re-epithelialisation in wound healing, have anti-inflammatory activity against UV-induced erythema and reduce itch (Ebner et al 2002). Under double-blind study conditions, epidermal wounds treated with dexpanthenol emulsion showed a reduction in erythema, and more elastic and solid tissue regeneration. Another randomised, prospective, double-blind, placebo-controlled study published in 2003 investigated the efficacy of topical dexpanthenol as a protectant against skin irritation. The study involved 25 healthy volunteers who were treated with a topical preparation containing 5% dexpanthenol or a placebo and then exposed to sodium lauryl sulphate 2% twice daily over 26 days. Treatment with topical dexpanthenol provided protection against skin irritation, whereas a statistically significant deterioration was observed in the placebo group (Biro et al 2003).

Although Bepanthen is commonly used in radiotherapy departments to ameliorate acute radiotherapy skin reactions, a prospective study of 86 patients undergoing radiotherapy showed that topical use of Bepanthen did not improve skin reactions under these conditions (Lokkevik et al 1996). Similarly, negative results were also obtained in an animal study by Dorr et al (2005).

Nasal spray

A RCT of 48 outpatients diagnosed with rhinitis sicca anterior found that dexpanthenol nasal spray is an effective symptomatic treatment for this condition (Kehrl & Sonnemann 1998). Two years later, another RCT compared the effects of xylometazoline-dexpanthenol nasal spray versus xylometazoline nasal spray over a 2-week period in 61 patients with rhinitis after nasal surgery (Kehrl & Sonnemann 2000); it showed that the combination of xylometazoline-dexpanthenol nasal spray was significantly superior to the other treatment and well tolerated.

More recent studies support this emerging trend and point towards a reduction in ciliary and cytotoxic effects from the nasal decongestants when 5% dexpanthenol is concurrently administered (Klocker et al 2003).

Elevated cholesterol and triglyceride levels

Several clinical studies confirm that pantethine, a metabolite of pantothenic acid, exerts significant lipid-lowering activity (Coronel et al 1991, Donati et al 1986, Gaddi et al 1984).

One double-blind study of 29 patients found that 300 mg of pantethine taken three times daily resulted

Clinical note — Could pantothenic acid be an anti-ageing nutrient?

A contemporary theory of ageing implicates mitochondrial functional decline, or 'oxidative decay' of the mitochondria, as a major contributor. In light of this hypothesis, nutrients that possess a critical role in the mitochondria are being re-examined to determine their ability to prevent ageing in humans. The focus has been on pantothenic acid, biotin, lipoic acid, iron and zinc, because deficiencies of these micronutrients have been implicated in increased mitochondrial oxidation (Ames et al 2005, Atamna 2004). In addition, those with antioxidant capabilities are of particular interest, such as pantothenic acid, lipoic acid and zinc.

Because of the numerous nutrients implicated in mitochondrial health and disease, a broad-based multivitamin should be considered instead of a single-nutrient supplement for populations at increased risk of poor nutrition, such as the elderly, young, poor and obese (Ames et al 2005).

in significant reductions to plasma total cholesterol, LDL cholesterol and triglycerides, and an increase in HDL cholesterol levels (Gaddi et al 1984).

A 2005 review analysed results from 28 clinical trials encompassing a pooled population of 646 hyperlipidaemic patients who were supplemented with a mean dose of 900 mg pantethine over an average trial length of 12.7 weeks. The results of these studies suggest a response to pantethine that is time-dependent, with progressively greater reductions in LDL cholesterol and triacylglycerols between month 1 and 9. The most impressive results were observed at 9 months, with a reduction of total cholesterol by 20.5%, LDL cholesterol by 27.6% and triacylglycerols by 36.5% from baseline. Although minor increases were observed in HDL levels in the early stages of most trials, longer-term studies suggested that this is not sustained.

Of the trials studied, 22 were conducted in Italy and all were conducted between 1981 and 1991. The authors point out that no further clinical trials were published, and concluded that evidence to date has yielded positive and promising results, and further research is warranted.

OTHER USES

Pantothenic acid has been used for many other indications, but controlled studies to determine whether treatment is effective are lacking.

Stress

As vitamin B_5 is essential for adrenal cortex function and the synthesis of steroid hormones, it is often used together with other B vitamins during times of stress in order to improve the body's response and restore nutrient levels. Interestingly, a large number of experiments in the 1950s attempted to elicit the impact of pantothenic acid deficiency on adrenal function and stress response in animals; however, little research has been done since. A small study demonstrated that injections of pantothenic acid in B_5-deficient rats corrected the deficiency and had a steroidogenous effect.

Inflammatory conditions

Pantothenic acid has been used as adjunctive treatment in inflammatory conditions such as asthma and dermatitis, with the intention of improving adrenal cortex output of hormones that have anti-inflammatory activity.

Clinical note — Could Vitamin B_5 prevent neural tube defects?

Ongoing evidence from animal studies suggests that pantothenic acid may have a preventative role against neural tube defects (NTDs) independent of folic acid (Dawson et al 2006). Pharmaceuticals such as valproic acid that increase the risk of NTD offspring have been shown also to reduce hepatic concentrations of CoA, an effect attenuated by co-administration of pantothenic acid. While the role of B_5 in neural tube closure remains unknown, it appears that it exerts actions both overlapping with and independent of folate.

Ergogenic aid

Based on its role in carbohydrate metabolism, vitamin B_5 has been used to increase stamina and athletic performance.

Reducing drug toxicity

Preliminary research in animal models shows that pantothenic acid reduces the toxicity effects of kanamycin and carbon tetrachloride and, when combined with carnitine, protects against valproate toxicity (Moiseenok et al 1984, Nagiel-Ostaszewski & Lau-Cam 1990, Thurston & Hauhart 1992).

Female alopecia

According to a study of 46 women with symptoms of diffuse alopecia, calcium pantothenate (200 mg/day) over 4–5 months does not cause a significant improvement in this condition (Brzezinska-Wcislo 2001).

DOSAGE RANGE

Australian ADI

- Women: 4 mg/day.
- Men: 6 mg/day.

According to clinical studies

- Wound healing: dexpanthenol cream 5% applied to affected areas up to two times daily.
- Lipid-lowering: pantethine 300 mg three times daily.

TOXICITY

No toxicity level known.

ADVERSE REACTIONS

Pantothenic acid is well tolerated, but contact dermatitis has been reported with topical dexpanthenol.

SIGNIFICANT INTERACTIONS

Antibiotics

Antibiotics will reduce endogenous production of vitamin B_5 by gastrointestinal flora. Increase vitamin B_5-rich foods or consider supplementation.

Oral contraceptive pill

Taking the OCP may increase the requirement for pantothenic acid. Increase vitamin B_5 rich foods or consider supplementation (Plesofsky 2002).

CONTRAINDICATIONS AND PRECAUTIONS

None known.

PREGNANCY USE

Considered safe when ingested at usual dietary doses.

PATIENTS' FAQs

What will this vitamin do for me?

Vitamin B_5 is essential for health and is used for many different conditions; for example, it is often used as part of a vitamin B complex supplement to aid the body during times of stress. In many of its uses research is not available to determine whether it is effective. Research generally supports its use in wound healing and in the form of pantethine to reduce cholesterol levels.

When will it start to work?
Pantethine reduces cholesterol levels within 2 months; however, optimal results are achieved with 9 months of supplementation. Xylometazoline-dexpanthenol nasal spray reduces symptoms of rhinitis within 2 weeks. It is not known how quickly the vitamin starts to work in most other conditions.

Are there any safety issues?
Pantothenic acid and pantethine are considered safe substances and are generally well tolerated.

PRACTICE POINTS/PATIENT COUNSELLING

- Deficiency is extremely rare, as pantothenic acid is widely distributed and present in nearly all plant and animal foods. Those at risk of reduced vitamin status are alcoholics, diabetics and people with malabsorption syndromes.
- Pantethine reduces total cholesterol levels significantly, according to controlled studies in both healthy and diabetic people.
- Dexpanthenol cream acts like a moisturiser, activates fibroblast proliferation, accelerates re-epithelialisation in wound healing, has anti-inflammatory activity against UV-induced erythema and reduces itch. When used in a nasal spray, it reduces symptoms of rhinitis.
- Vitamin B_5 supplements are commonly used together with other B vitamins during times of stress in order to improve the body's response and restore nutrient levels.
- Vitamin B_5 has also been used as adjunctive treatment for inflammatory conditions such as dermatitis and asthma, as an ergogenic aid, to treat alopecia and to restore colour to greying hair, although no controlled studies are available to determine effectiveness in these conditions.

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Vitamin B_6

BACKGROUND AND RELEVANT PHARMACOKINETICS

Vitamin B_6 was discovered in 1938. Absorption of vitamin B_6, also known as pyridoxine, takes place in the jejunum by a passive, non-saturable process. The more acidic the environment, the greater is the absorption. It is transported in the plasma and red blood cells to the liver, where it is converted to pyridoxal 5′ -phosphate, and is then available to other tissues. It is mainly stored in muscle tissue, and ultimately metabolised and excreted via the kidneys.

CHEMICAL COMPONENTS

Vitamin B_6 is a water-soluble vitamin and has six forms, of which pyridoxine hydrochloride is the main form found in supplements and used to fortify foods. Pyridoxine is the alcohol form, pyridoxal the aldehydic form and pyridoxamine the amine form. Each has a 5′-phosphate derivative.

FOOD SOURCES

Vitamin B_6 is widely distributed in animal and plant foods. The best food sources are fish, organ meats, legumes, wheatgerm, eggs, nuts, potatoes and bananas. Per milligram, Vegemite is one of the richest sources.

Up to 40% can be lost through cooking (Wahlqvist et al 1997).

DEFICIENCY SIGNS AND SYMPTOMS

Clinical signs and symptoms are non-specific because this vitamin is necessary for the proper functioning of over 60 enzymes (Pelton et al 2000, Wahlqvist et al 1997). In adults with B_6 deficiency, chiefly dermatological, circulatory and neurological changes develop. In children, the central nervous system is also affected.

- dermatitis (similar to that seen in pellagra)
- angular stomatitis and glossitis, and cheilosis
- sideroblastic anaemia
- impaired antibody production
- renal calculi
- elevated homocysteine levels (Lakshmi & Ramalakshmi 1998)
- CNS effects such as irritability, confusion, lethargy, clinical depression, elevated seizure activity (particularly in children), abnormal brain wave patterns and nerve conduction
- birth defects such as cleft palate (associated with elevated homocysteine) (Weingaertner et al 2005)

Pyridoxine deficiency has also been associated with premature coronary artery disease and with impaired oxidative defence mechanisms (Miner et al 2001).

Primary deficiency

Primary deficiency is rare because this vitamin is widely available in many foods. Groups at risk of deficiency include breastfed babies born with low plasma B_6 levels, the elderly, people who consume large quantities of alcohol and people on dialysis due to abnormal vitamin loss (Groff & Gropper 2009).

Secondary deficiency

This may result from malabsorption syndromes, cancer, liver cirrhosis and alcoholism, hyperthyroidism, congestive heart failure or medicine use (such as the oral contraceptive pill), isoniazid, hydralazine, penicillamine, theophylline or monoamine oxidase (MAO) inhibitors (Beers & Berkow 2003, Bratman & Kroll 2000, Wardlaw 1997).

MAIN ACTIONS

Coenzyme

Vitamin B_6 is an important coenzyme in the biosynthesis of the neurotransmitters GABA, dopamine and serotonin (Gerster 1996). It is also involved in protein metabolism, haemoglobin synthesis, gluconeogenesis, lipid metabolism, niacin formation, immune system processes, nucleic acid synthesis and hormone modulation (Bratman & Kroll 2000, Wardlaw 1997).

Clinical note — Marginal B_6 deficiency

Although frank deficiency is rare, marginal deficiency appears to be common. One study found that 100% of 174 university students tested had some degree of vitamin B_6 deficiency (Shizukuishi et al 1981). A larger survey of 11,658 adults found that 71% of males and 90% of females did not meet the RDI requirements for B_6 (Kant & Block 1990).

Homocysteine

Homocysteine is formed from the essential amino acid methionine and about 50% is then remethylated to methionine via steps that require folic acid and vitamin B_{12}. Vitamin B_6 is required for another metabolic pathway and is a cofactor for cystathionine beta-synthase, which mediates the transformation of homocysteine to cystathionine (Wilcken & Wilcken 1998).

Serotonin

Pyridoxine is required for the synthesis of many neurotransmitters, including serotonin. It is a cofactor for the enzyme 5-hydroxytryptophan decarboxylase, which is involved in one of the steps that converts tryptophan to serotonin (Pelton et al 2000). Deficiency states are therefore associated with alterations to mood and other psychological disturbances.

Antioxidant

B_6 has been shown both in vitro and in vivo to display antioxidant activity (Kannan & Jain 2004, Anand 2005, Ji et al 2006, Matxain et al 2007).

Antitumour

In vitro and in vivo experiments have found evidence of some antitumour action on a number of cell lines, including breast and pituitary cells (Shimada et al 2005, Ren & Melmed 2006, Shimada et al 2006).

Reducing diabetic complications

According to Jain et al (2007), animal studies show that B_6 may reduce the incidence of several diabetic complications, such as retinopathy, nephropathy and dyslipidaemia. It is thought that advanced glycation end-products (AGEs) contribute to the development of diabetic nephropathy and other diabetes complications, and according to in vivo research, pyridoxamine (from the B_6 group of compounds) exerts antioxidant and anti-AGE action in the kidneys (Tanimoto et al 2007). The anti-AGE action of pyridoxal phosphate was confirmed in a diabetic rat model, where it prevented the progression of nephropathy (Nakamura et al 2007).

OTHER ACTIONS

Pyridoxine displayed a protective effect against neurotoxicity induced by glutamate in vivo, which may prove useful in hypoxic-ischaemic brain injury (Buyukokuroglu et al 2007). Another animal study indicated that neuroprotective activity preventing ischaemic damage may be due to a gamma aminobutyric acid (GABA) inhibitory effect (Hwang et al 2007).

Immune stimulant actions, with an increase in T-helper and T-lymphocyte cells, were found in critically ill patients to whom B_6 was administered (Cheng et al 2006).

CLINICAL USE

Vitamin B_6 supplementation is used to treat a large variety of conditions and is mostly prescribed in combination with other B group vitamins.

Deficiency

It is traditionally used to treat vitamin B_6 deficiency.

Premenstrual syndrome (PMS)

Vitamin B_6 supplementation is used in doses beyond RDI levels for the treatment of PMS. A 1999 systematic review of nine clinical trials involving 940 patients with PMS supports this use, finding that doses up to 100 mg/day are likely to be of benefit in treating symptoms and PMS-related depression (Wyatt et al 1999). Another recent double-blind RCT of 94 patients taking a dose of 40 mg B_6 twice a day found active treatment significantly decreased PMS symptoms during the second cycle. Benefits were most pronounced for mood and psychiatric symptoms (Kashanian et al 2008).

Comparative study

One randomised double-blind study compared the effects of pyridoxine (300 mg/day), alprazolam (0.75 mg/day), fluoxetine (10 mg/day) or propranolol (20 mg/day) in four groups of 30 women with severe PMS (Diegoli et al 1998). In this study, fluoxetine produced the best results (a mean reduction of 65.4% in symptoms), followed by propanolol (58.7%), alprazolam (55.6%), pyridoxine (45.3%) and the placebo (39.4–46.1%). Symptoms responding well to pyridoxine were tachycardia, insomnia, acne and nausea (Diegoli et al 1998). Another comparative study of 60 women tested 100 mg of B_6 against bromocriptine and a placebo over 3 months. Both active treatments produced a significant reduction in symptoms compared to the control group; however, vitamin B_6 treatment was slightly more effective than bromocriptine and produced fewer side effects (Sharma et al 2007).

Morning sickness

A Cochrane Review in 2000 of 23 randomised trials investigating all treatments for morning sickness concluded that pyridoxine significantly reduces the severity of morning sickness (Jewell & Young 2002). More recent research supports this finding. A well designed, double-blind, randomised, controlled trial found 55% of women receiving B_6 supplements experienced a significant subjective improvement in symptoms over a 3-week period compared to the placebo (Smith & Crowther 2005). Other clinical trials comparing B_6 and ginger have concluded that both are effective in reducing nausea in pregnancy (Ensiyeh & Sakineh in press, Chittumma et al 2007).

Heart disease

Elevated homocysteine (Hcy) levels

In practice, the relative safety and affordability of combined vitamin B supplementation (B_{12}, folic acid and B_6) make it an attractive recommendation in people with familial hyperhomocysteinaemia. Whether lowering total Hcy improves cardiovascular mortality and morbidity is questionable, as recent large-scale clinical trials and meta-analyses have failed to demonstrate any benefits for B group vitamins (including B_6) in reducing overall cardiovascular risk, despite showing a reduction in homocysteine levels (Albert et al 2008, Clarke et al 2007, CTSUESU 2006, den Heijer et al 2007, Mann et al 2008, Marcus et al 2007, Ray et al 2007). Failure of combined B vitamin therapy to reverse inflammatory processes associated with atherogenesis may partly explain the negative results (Bleie et al 2007). The consistent findings of an association between elevated plasma total Hcy levels and vascular risk is yet to be fully explained; however, it is possible that the association is a consequence rather than a cause of disease (Toole et al 2004).

Reducing thromboembolism

A prospective cohort study of 757 patients experiencing first venous thromboembolism found that patients with lower plasma B_6 had a 1.8-fold higher risk of recurrence than those with higher levels of B_6 (Hron et al 2007). In contrast, no risk reduction was found in a secondary analysis of (HOPE)-2 trial which included over 5,000 individuals with known cardiovascular disease or diabetes who were given a daily supplement of folic acid (2.5 mg), B_6 (50 mg) and B_{12} (1 mg) or a placebo for 5 years. In this analysis, vitamin therapy reduced Hcy levels; however, it did not reduce the risk of venous thromboembolism, deep vein thrombosis or pulmonary embolism (Ray et al 2007).

Improving outcomes after heart transplantation

Cardiac transplantation represents a potentially life-saving procedure for patients with end-stage cardiac disease. Short-term survival is improving because of improved immunosuppression, but long-term survival remains limited by an aggressive form of atherosclerosis known as transplant coronary artery disease (Miner et al 2001).

A randomised, double-blind placebo-controlled study showed that pyridoxine supplementation (100 mg/day) taken for 10 weeks improved endothelial function as assessed by flow-mediated dilatation in cardiac transplant recipients (Miner et al 2001). Interestingly, homocysteine levels remained unchanged with treatment, suggesting other mechanisms are responsible.

Improving other cardiovascular risk factors

A randomised, double blind, placebo controlled study of 50 patients who were perceived to be at risk of cerebral ischaemia received B_6 (25 mg), folate (2.5 mg) and B_{12} (0.5 mg) or a placebo daily for a year. The study found supplementation significantly reduced carotid intima-media thickness, which is a marker of atherosclerotic changes (Till et al 2005). In contrast, another small, double-blind, randomised and placebo-controlled trial of 30 individuals with a history of ischaemic stroke found that long-term treatment over 3.9 years with similar dosages of B_6 and B_{12} to the previous trial and slightly less folate (2 mg) produced no differences in carotid intima-media thickness and endothelial function (Potter et al 2007).

Bladder cancer

In an attempt to find a link between dietary components and incidence of bladder cancer, diet was assessed for 912 patients with bladder cancer and 873 controls by Garcia-Closas et al (2007). Individuals in the highest quintile for B_6 intake had a 40% reduced risk of bladder cancer compared with those in the lowest quintile.

Colorectal cancer

Current evidence suggests high dietary vitamin B_6 intake is associated with a reduced risk of colorectal cancer. One large longitudinal population study ($n = 61$; 433 women aged 40–76 years) used a food-frequency questionnaire with a follow-up over 14.8 years and found that high dietary vitamin B_6 was associated with lower colorectal cancer risk, with protective effects most notably seen in women who drank alcohol (Larsson et al 2005). Similarly, a case control study of 2,028 people with colorectal cancer and 2,722 controls confirmed a dose-dependent protective effect of B_6, with strongest protective effects observed for the highest intake and in people aged over 55 years (Theodoratou et al 2008). Another large population study of both men and women further confirmed that low dietary B_6 was associated with an increased risk in colorectal cancer, but the effect was specific for men and not for women. Protective effects were strongest in men with higher alcohol intake. These findings were from the large Japan Public Health Center-based Prospective Study, from which there were 526 cases of colorectal cancer (Ishihara et al 2007). An RCT also found that high levels of plasma B_6 may be protective against colorectal adenomas (Figueiredo et al 2008).

Carpal tunnel syndrome

It has been suspected that vitamin B_6 deficiency may play a role in the development of carpal tunnel syndrome (CTS) as several studies have found that patients with CTS and pyridoxine deficiency respond to supplementation (Ellis et al 1991). More recent evidence now casts doubt on the usefulness of B_6 supplementation in CTS. A 2002 review found no benefit with pyridoxine treatment in CTS (Gerritsen et al 2002). Similarly, a 2007 systematic review of treatments for CTS concluded that there was moderately strong evidence to suggest that B_6 was ineffective in the treatment of the condition (Piazzini et al 2007).

Autism

High-dose pyridoxine and magnesium supplementation is a popular nutritional treatment in autism, although current evidence is contradictory. A critical analysis of 12 published studies concluded that evidence generally supports the efficacy of vitamin treatment; however, there were methodological shortcomings inherent in many of the studies (Pfeiffer et al 1995). Other more recent studies also support the use of a combination treatment of magnesium and B_6 for improving symptoms such as social interaction, communication and general behaviour in autism (Mousain-Bosc et al 2006). It is suspected that some autistic individuals may benefit from B_6 supplementation as a result of an impairment of the conversion of pyridoxine and pyridoxal to pyridoxal 5 phosphate (Adams et al 2006).

In contrast, a small, 10-week, double-blind, placebo-controlled trial found that an average dose of 638.9 mg pyridoxine and 216.3 mg magnesium oxide was ineffective in ameliorating autistic behaviours (Findling et al 1997). In 2006, a systematic review found that the quality and small sizes of the studies posed problems in evaluating the evidence that led to their conclusion that B_6-Mg therapy could not be recommended (Nye & Brice 2005).

Convulsions during a febrile episode

Two randomised trials have been conducted in children, producing conflicting results. One study of 65 children who had been admitted to hospital with febrile convulsions showed that a dose of 2–10 mg/kg pyridoxal phosphate daily (PO or IV) produced a 100% success rate, whereas 43% in the control group experienced repeated convulsions (Kamiishi et al 1996). A second randomised trial found that a lower dose of 20 mg twice daily did not alter the incidence of febrile convulsions compared with placebo (McKiernan et al 1981).

Symptomatic treatment for stress

The term 'stress', as used by the public, is a subjective one and often described in different ways. One theoretical model that has been developed to predict psychological stress includes measures of life stressors, social support and coping style. Using this model, pyridoxine deficiency has been identified as a significant predictor of increased overall psychological stress during bereavement. More specifically, pyridoxine deficiency is significantly associated with increases in depression, fatigue and confused mood levels, but not with those of anxiety, anger or vigour (Baldewicz et al 1998).

One explanation is that pyridoxine is involved in neurotransmitter biosynthesis, such as GABA and serotonin, and therefore deficiency states that are associated with mood disturbances are improved with consequent supplementation (McCarty 2000).

Cognitive performance/Alzheimer's disease

Whether vitamin B_6 supplementation provides benefits in cognitive function and Alzheimer's disease (AD) remains to be clarified. It has gained some attention as a cheap and safe method of reducing homocysteine, which is implicated in the aetiology of AD and cognitive dysfunction; however, findings are equivocal.

One systematic review evaluated data from 16 studies that investigated the association between cognitive function in the elderly and B_6, folate and B_{12}. An association was found between folate and cognition in AD, but no association was found for vitamins B_6 or B_{12}. However, the authors suggested that heterogeneity in the methodology of the studies made interpretation problematic (Raman et al 2007).

A similar research group doing a systematic review of 14 trials found that most studies were small and of low quality. They found that three studies of B_6 and six trials of combined B vitamins revealed no effect, despite different dosages, on cognitive function. Only one of the trials found a significant improvement using B_6 to improve long-term memory. The review concluded that there was insufficient evidence to support a positive effect of B_6 on cognition. The reviewers suggested that larger, well designed trials are needed to assess different groups of the population for any association between B_6 and cognitive function (Balk et al 2007).

Homocysteine and AD

According to one systematic review published in 2008, evidence is strong to suggest high homocysteine is a risk factor for AD and further randomised controlled trials are warranted to evaluate the association between B_6, folate, B_{12}, homocysteine levels and AD (Van Dam & Van Gool 2008).

Brain matter

Investigation of a healthy elderly population found a relationship between greater B_6 supplement intake and greater grey matter volume (Erickson et al 2008). Another study with Alzheimer's patients found that low B_6 levels in patients were associated with white matter lesions in the brain (Mulder et al 2005). The clinical significance of these findings remains to be clarified.

It has also been theorised that inflammation may be implicated in AD and dementia and that C-reactive protein (CRP), as a marker for systemic inflammation, may be a risk factor. A study of 85 individuals discovered that, where CRP was elevated, this was related to low B_6 levels and cerebral atrophy (Diaz-Arrastia et al 2006). This anti-inflammatory effect of B_6 may explain its possible role in neurodegenerative diseases; another interesting observation came from a study with older men, where levels of beta amyloid levels were reduced with B_6, folate and B_{12} (Flicker et al 2008).

Schizophrenia

It has been suggested that high levels of homocysteine (Hcy) contribute to the pathogenesis of schizophrenia and the complex metabolic regulation of Hcy that could be disrupted in schizophrenia (Petronijevic et al 2008).

To test whether supplementation could benefit this population, Levine et al (2006) conducted an RCT of 42 schizophrenic patients with plasma Hcy levels > 15 micromol/L. Treatment with oral folic acid, vitamin B_{12} and pyridoxine for 3 months reduced Hcy and, more importantly, significantly improved clinical symptoms as measured by the Positive and Negative Syndrome Scale and neuropsychological tests overall, in particular the Wisconsin Card Sort (Levine et al 2006).

Tardive dyskinesia (TD)

Tardive dyskinesia is a significant clinical problem. Vitamin B_6 is a potent antioxidant and has a role in almost all of the possible mechanisms that are thought to be associated with appearance of TD (Lerner et al 2007). To test whether supplementation would have any benefits, a 26-week, double-blind, placebo-controlled trial was conducted with 50 inpatients who had DSM-IV diagnoses of schizophrenia or schizoaffective disorder and TD. The randomised study found treatment with vitamin B_6 (1200 mg/day) significantly reduced symptoms of TD compared to a placebo.

Parkinson's disease (PD)

A higher dietary intake of vitamin B_6 was associated with a significantly decreased risk of PD, probably through mechanisms unrelated to homocysteine metabolism according to findings from the Rotterdam Study — a prospective, population-based cohort study of people aged 55 years and older (de Lau et al 2006). The association between dietary intake of folate, vitamin B_{12} and vitamin B_6 and the risk of incident PD among 5,289 participants was evaluated. After a mean follow-up of 9.7 years, the authors identified 72 participants with incident PD. Stratified analyses showed that this association was restricted to smokers. No association was observed for dietary folate and vitamin B_{12}.

Hyperhomocysteinaemia has been reported repeatedly in PD patients; the increase, however, seems mostly related to the methylated catabolism of l-Dopa, the main pharmacological treatment of PD (Martignoni et al 2007).

OTHER USES

Vitamin B_6 supplements are effective for treating hereditary sideroblastic anaemia and refractory seizures in newborns, caused by pyridoxine withdrawal after delivery. Vitamin B_6 supplements have been used to prevent diabetic retinopathy and kidney stones, and to treat symptoms of vertigo, allergy to monosodium glutamate, asthma, photosensitivity and pervasive developmental disorders with hypersensitivity to sound. Women taking the oral contraceptive pill sometimes use supplemental B_6 to relieve mood disturbances and restore vitamin status.

A small trial has shown some future potential clinical use in renal transplant patients with high Hcy levels and endothelial dysfunction. A dose of folate (5 mg/day), B_6 (50 mg/day) and B_{12} (1000 microgram/day) was given to stable renal transplant

patients for 6 months and Hcy levels decreased and endothelial function was improved compared to the control patients (Xu et al 2008). Further trials are needed to confirm this finding.

Dream states

Many have suspected that pyridoxine supplements taken at night are able to influence dream states and sleep, causing disruption in some people. The results of a 2002 double-blind, placebo-controlled crossover study support this observation (Ebben et al 2002). Pyridoxine supplementation (250 mg) taken before bedtime was shown to significantly influence dream-salience scores (a composite score containing measures for vividness, bizarreness, emotionality and colour), starting on the first night of treatment.

Leg cramps during pregnancy

A study of 84 pregnant women with leg cramps found that a combination of vitamin B_1 (100 mg/day) and B_6 (40 mg/day) improved symptoms 7.5 fold, and this was a better result than given by treatment with calcium carbonate (Sohrabvand et al 2006).

DOSAGE RANGE

- Prevention of deficiency: Australian RDI for adults and children > 8 years: 1–1.7 mg/day.
- Treatment of deficiency: 5–25 mg/day.
- Morning sickness: 30–75 mg/day, sometimes taken as 25 mg three times daily.
- Symptoms of PMS: 100–500 mg/day.
- Elevated homocysteine levels: 100 mg/day (usually taken with B_{12} and folic acid).
- Leg cramps in pregnancy: vitamin B_1 100 mg/day and B_6 40 mg/day.
- Schizophrenic people with tardive dyskinesia: vitamin B_6 (1200 mg/day).

TOXICITY

Symptoms of toxicity include paraesthesia, hyperaesthesia, bone pain, muscle weakness, numbness and fasciculation, most marked at the extremities (Dalton & Dalton 1987, Diegoli et al 1998). Some symptoms include unsteady gait, numbness of the hands and feet, impaired tendon reflexes. Excessive doses of vitamin B_6 cause degeneration of the dorsal root ganglia in the spinal cord, loss of myelination and degeneration of sensory fibres in the peripheral nerves.

The dose and time frame at which toxicity occurs vary significantly between individuals. Studies involving large population groups using 100–150 mg/day have shown minimal or no toxicity in 5- to 10-year studies, whereas studies of women self-medicating for PMS, taking 117 ± 92 mg for 2.9 ± 1.9 years, have reported increased incidence of peripheral neuropathy (Bernstein 1990, Dalton & Dalton 1987).

ADVERSE REACTIONS

Pyridoxine is considered non-toxic, although nausea and vomiting, headache, paraesthesia, sleepiness and low-serum folic acid levels have been reported.

Supplements taken at night may result in more vivid dreams and, for some individuals, disrupted sleep (Ebben et al 2002).

SIGNIFICANT INTERACTIONS

Amiodarone

Pyridoxine may increase the risk of drug-induced photosensitivity. Exercise caution with patients taking pyridoxine and amiodarone concurrently.

Antibiotics

Destruction of gastrointestinal flora can decrease endogenous production of vitamin B_6. Increase intake of vitamin B_6-rich foods or consider supplementation with long-term drug treatment.

Hydralazine

Hydralazine may induce B_6 deficiency according to a clinical study. Increased intake may be required with long-term drug therapy.

Isoniazid

Isoniazid increases vitamin B_6 requirements. Increase intake of vitamin B_6-rich foods or consider supplementation with long-term drug treatment.

L-Dopa (without carbidopa)

In people with Parkinson's disease, L-dopa can cause hyperhomocysteinaemia, the extent of which is influenced by B-vitamin status. To maintain normal plasma homocysteine concentrations, the B-vitamin requirements are higher in L-dopa-treated patients than in those not on L-dopa therapy. B-vitamin supplements may be warranted for PD patients on L-dopa therapy (Miller et al 2003)

Oral contraceptives

Oral contraceptives increase vitamin B_6 requirements. Increase intake of vitamin B_6-rich foods or consider supplementation with long-term drug treatment.

Penicillamine

This drug increases vitamin B_6 requirements. Increase intake of vitamin B_6-rich foods or consider supplementation.

Phenobarbitone, phenytoin

Vitamin B_6 supplements may lower plasma levels and efficacy of these drugs. Monitor for drug effectiveness, and exercise caution when these drugs are being taken concurrently.

Theophylline

May induce pyridoxine deficiency. Increased intake may be required with long-term drug therapy.

CONTRAINDICATIONS AND PRECAUTIONS

Monitor long-term use of high-dose pyridoxine supplements (> 100 mg, although this level varies between individuals).

PREGNANCY USE

Pyridoxine supplements are commonly used during pregnancy to reduce symptoms of morning sickness, suggesting safety when used in appropriate doses.

PRACTICE POINTS/PATIENT COUNSELLING

- Vitamin B_6 is available in many foods; however, several surveys suggest that inadequate intakes are common.
- Deficiency can manifest with psychological symptoms of depression, irritability and confusion, and physical symptoms of lethargy, dermatitis, angular stomatitis, glossitis and impaired immunity.
- Overall, clinical research supports the use of vitamin B_6 supplements in relieving mild-to-moderate symptoms of PMS (particularly breast tenderness and mood disturbance), nausea in pregnancy and as a treatment for hyperhomocysteinaemia.
- Preliminary evidence suggests regular dietary B_6 in levels above the RDA may have a protective effect in colorectal cancer, bladder cancer risk and incidence of Parkinson's disease.
- There is conflicting evidence as to whether vitamin B_6 supplements improve symptoms of carpal tunnel syndrome and autism (combined with magnesium), and whether they prevent febrile convulsions in children.
- Pyridoxine should not be used in high doses for the long term, as this can induce toxicity.

PATIENTS' FAQs

What will this vitamin do for me?

Vitamin B_6 is essential for the body's normal functioning. It has been used to treat many different conditions; however, scientific evidence generally supports its use in only a few conditions (e.g. morning sickness, mild-to-moderate PMS and elevated homocysteine levels).

When will it start to work?

This will depend on what is being treated. With regard to PMS symptoms, effects may take two to three menstrual cycles, whereas for morning sickness effects can be seen within two to three days.

Are there any safety issues?

High doses should not be taken for the long term, as this can cause toxicity.

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Vitamin B_{12}

BACKGROUND AND RELEVANT PHARMACOKINETICS

Vitamin B_{12} (cobalamin) is a water-soluble vitamin obtained mostly from animal protein products in the diet. In the stomach gastric acid is required to liberate protein-bound cobalamin, which is then immediately bound to R-binders (glycoproteins) that protect it from being denatured. When the contents of the stomach reach the duodenum, the R-binders are partially digested by pancreatic proteases, releasing them to bind to intrinsic factor (a glycoprotein), which is secreted by the parietal cells of the gastric mucosa. This complex is then absorbed in the terminal ileum and transported to cells, where it carries out its metabolic function, or to the liver, where it is stored until required (FAO/WHO 2002, Oh & Brown 2003). An alternative method of absorption, which is independent of intrinsic factor, also appears to exist and accounts for the absorption of approximately 1% of large oral doses (> 300 μg) of B_{12} (Elia 1998). Absorption via intrinsic factor is limited to about 1.5–2.0 μg/meal owing to limited receptor capacity (FAO/WHO 2002).

CHEMICAL COMPONENTS

Vitamin B_{12} is the largest of the B vitamins and is a complex structure containing a central cobalt atom. There are five forms of B_{12}: cyanocobalamin (a synthetic form that has a cyanide attached to the cobalt), hydroxycobalamin (hydroxyl group attached to the cobalt; it is produced for parenteral administration), aquacobalamin (water group bound to the cobalt) and the coenzymatically active forms (methylcobalamin and 5-deoxyadenosylcobalamin), in which a methyl group or a 5-deoxyadenosyl group is bound to the cobalt atom (FAO/WHO 2002, Freeman et al 1999).

FOOD SOURCES

Lambs liver, sardines, oysters, egg yolk, fish, beef, kidney, cheese and milk. Up to 10% is lost in cooking (Wahlqvist 2002). Fortified breakfast cereals are also becoming increasingly available.

Vitamin B_{12} bioavailability significantly decreases with increasing intake as the intrinsic factor-mediated intestinal absorption system is estimated to be saturated at about 1.5–2.0 μg/meal for healthy adults with normal gastrointestinal function. The bioavailability of vitamin B_{12} from different sources is variable: fish (42%), lamb (56–89%), chicken (61–66%), eggs (< 9%) (Watanabe 2007).

Plants do not contain B_{12} because they have no cobalamin-dependent enzymes (Croft et al 2005). Most microorganisms, including bacteria and algae, synthesise B_{12}, which then makes its way into the food chain (FAO/WHO 2002). Human intestinal bacteria also synthesise B_{12}, but this is not absorbed to any considerable extent (Wahlqvist 2002). Vegans living in situations with more stringent hygiene are therefore more likely to develop deficiencies.

Clinical note — Nori: a source for vegetarians

Rat studies have demonstrated improvements in B_{12} status following the ingestion of nori (seaweed). Nori is said to contain as much B_{12} as liver (Croft et al 2005) approximately 55–59 μg/100 g dry weight. Five different biologically active vitamin B_{12} compounds have been identified in nori: cyanocobalamin, hydroxycobalamin, sulfitocobalamin, adenosylcobalamin and methylcobalamin (Takenaka et al 2001); the source of B_{12} appears to be bacteria (Croft et al 2005).

DEFICIENCY SIGNS AND SYMPTOMS

Vitamin B_{12} deficiencies manifest primarily as haematological and neurological disturbances, and are estimated to affect 10–15% of individuals over the age of 60 years (Baik & Russell 1999).

- Haemotological: macrocytic (megaloblastic) anaemia, pancytopenia (leukopenia, thrombocytopenia); symptoms may include lethargy, dyspnoea, anorexia, weight loss and pallor (Wahlqvist 2002).
- Neurological disturbances: paraesthesias, optic neuropathy (reversible), peripheral neuropathy and demyelination of the corticospinal tract and dorsal columns (subacute combined systems disease).
- Psychological disturbances: impaired memory, irritability, depression, personality change, dementia and psychosis (Lee 1999, Lindenbaum et al 1988).
- Various gastrointestinal symptoms can also develop, such as loss of appetite, intermittent constipation and diarrhoea, glossitis and abdominal pain.
- Folic acid supplementation may mask an underlying B_{12} deficiency, leading to the progression of neurological symptoms.

Primary deficiency

People at risk are those living in India, Central and South America, and selected areas in Africa (Stabler & Allen 2004), strict vegetarians and vegans, breastfed infants of vegetarian mothers with low B_{12} stores, elderly patients with 'tea and toast diets' and chronic alcoholics. As vitamin B_{12} is stored to a considerable extent, even after complete depletion of food-ingested cobalamin, clinically relevant deficiencies will usually only develop after 5–10 years (Schenk et al 1999). This time frame increases to an average of approximately 18 years in strict vegetarians when intrinsic factor secretion is intact (Babior 1996). In this case, some enterohepatic recycling of cobalamin should occur in the distal ileum (Howden 2000).

Secondary deficiency

Vitamin B_{12} deficiency is more likely to result from inadequate absorption, defects in vitamin B_{12} metabolism or gastrointestinal disorders than a lack of dietary intake.

Clinical note — Testing for vitamin B_{12} deficiency

Numerous studies have indicated that serum B_{12} levels are an inadequate guide to B_{12} status (Briddon 2003, Carmel 1988, Kapadia 2000, Karnaze & Carmel 1990, Termanini et al 1998). The use of this test has led to poorly defined reference intervals for serum B_{12} (Briddon 2003), potentially delaying the diagnosis and allowing the progression of B_{12} deficiency. Approximately 50% of patients with subclinical disease have normal serum B_{12} levels and older patients present with neurological and psychiatric symptoms without haemotological findings. In addition, use of the oral contraceptive pill may also affect test results (Bor 2004). As a result, this method of testing has lost favour as an adequate measure of B_{12} status. A combination of two tests appears to be more conclusive. Elevated levels of total homocysteine in serum and plasma reflects deficiencies of either folate or B_{12}. MMA is a more specific marker of cobalamin function, but renal insufficiency may affect the results of this test. Therefore, a combination of the two is probably the clearest indicator (Bjorke Monsen & Ueland 2003, FAO/WHO 2002, Kapadia 2000). Preliminary evidence also suggests that overnight fasting urinary MMA concentrations correlate strongly with serum MMA; however, further investigations are required to confirm the application of this test in various populations (Kwok et al 2004). While the use of such markers may improve the assessment of B_{12} deficiency, establishing the cause of deficiency should also be part of the diagnostic approach (Schneede & Ueland 2005).

- Pernicious anaemia: an autoimmune condition affecting gastric parietal cells that produce intrinsic factor; common cause of megaloblastic anaemia, especially in persons of European or African descent (Stabler & Allen 2004).
- Methylmalonic acidaemia: inherited defect in B_{12} metabolism.
- Congenital absence of transcobalamin II.
- Medications that reduce gastric acidity (e.g. H_2 blockers and PPI).
- Atrophic gastritis/gastric atrophy: probably due to a decrease in acid output and intrinsic factor production (Schenk et al 1999). Gastric atrophy is more common in the elderly.
- Intestinal resection of the part of the ileum where absorption takes place or gastric resection, which affects the parietal cells and in turn production of intrinsic factor.
- Achlorhydria (Termanini et al 1998).
- Pancreatic insufficiency: the cobalamin-R-protein complex is split by pancreatic enzymes in the duodenum (Festen et al 1991).
- Ileal dysfunction (Howden 2000): may affect absorption at this site.
- Crohn's disease, irritable bowel disease, coeliac disease: reduced absorption.
- Bacteria and parasites in the intestine may also compete for B_{12}.
- Radiotherapy for rectal cancer: causes a rapid and persistent decrease in B_{12} status as reflected by reduced serum B_{12} combined with increased serum methylmalonic acid (MMA) (Gronlie Guren et al 2004).

The elderly deserve a separate mention as a population at risk of deficiency because of both primary and secondary causes, such as poor dietary intakes, failure to separate vitamin B_{12} from food protein, inadequate absorption, utilisation and storage, as well as drug–food interactions leading to malabsorption and metabolic inactivation (Bradford & Taylor 1999, Dharmarajan et al 2003). Subtle signs of deficiency may include lethargy, weight loss and dementia (Dharmarajan et al 2003).

Elevated levels of serum cobalamin may be a sign of a serious, even life-threatening, disease such as chronic myelogenous leukaemia, promyelocytic leukaemia, polycythaemia vera, hypereosinophilic syndrome, acute hepatitis, cirrhosis, hepatocellular carcinoma and metastatic liver disease. Elevated B_{12} levels, therefore, warrant a full diagnostic work up to assess the presence of disease (Ermens et al 2003).

MAIN ACTIONS

Important cofactor

Vitamin B_{12} is essential for the normal function of all cells. It affects cell growth and replication, the metabolism of carbohydrates, lipids and protein and is involved in fatty acid and nucleic acid synthesis. It is also involved in the production of red blood cells in bone marrow, and activates folacin coenzymes for red blood cell production.

Homocysteine reduction

Methylcobalamin aids in the conversion of homocysteine to methionine by the action of methionine synthase, transferring a methyl group from methylfolate (folic acid).

After conversion from homocysteine, methionine is then converted to *S*-adenosyl-L-methionine (SAMe), important for methylation reactions and protein synthesis. An increase in homocysteine levels and decrease in SAMe levels have been implicated in depression and may also contribute to the neurological symptoms seen in pernicious anaemia (IMG 2003).

Nervous system

Vitamin B_{12} is involved in the synthesis of protein structures in the myelin sheath and nerve cells. As methylation is required for the production of myelin basic protein, a reduction in B_{12} and SAMe will result in demyelination of peripheral nerves and the spinal column (subacute combined degeneration) (FAO/WHO 2002).

Immune system

Vitamin B_{12} acts as an immunomodulator for cellular immunity (Tamura et al 1999).

Liver

Vitamin B_{12} deficiency results in decreased serine dehydratase (SDH) and tyrosine aminotransferase (TAT) activities in rat livers (Ebara et al 2008). In dimethylnitrosamine-induced liver injury in mice, vitamin B_{12} decreased the blood levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) suggesting a possible hepatoprotective effect (Isoda et al 2008).

CLINICAL USE

Vitamin B_{12} supplementation is administered using various routes such as intravenous and oral doses. This review will focus on oral supplementation as this is the form generally used by the public and available OTC.

Deficiency: treatment and prevention

Traditionally, vitamin B_{12} supplementation has been used to treat deficiency or prevent deficiency in conditions such as pernicious anaemia and atrophic gastritis, but special consideration should be given to the elderly who are at high risk.

Pernicious anaemia

Pernicious anaemia is caused by a deficiency of intrinsic factor leading to malabsorption of vitamin B_{12}. Signs and symptoms include pallor, glossitis, weakness and neurological symptoms including paraesthesias of the hands and feet, decreased deep-tendon reflexes and loss of sensory perception and motor controls (neurological symptoms may be irreversible). In more progressed conditions confusion, memory loss, moodiness, psychosis and delusional behaviour may be present. Achlorhydria and gastric mucosal atrophy may also occur, further complicating the condition.

Uncomplicated pernicious anaemia is characterised by mild or moderate megaloblastic anaemia without leukopenia, thrombocytopenia or neurologic symptoms. In more advanced cases urgent parenteral administration of vitamin B_{12} and folic acid (typically 100 μg of cyanocobalamin and 1–5 mg of folic acid) is given intramuscularly, as well as blood transfusions.

Atrophic gastritis

Elderly patients with atrophic gastritis appear to have higher rates of vitamin B_{12} deficiency ($P < 0.01$) which responds to B_{12} supplementation (Lewerin et al 2008).

Infants

In infants, severe vitamin B_{12} deficiency can cause neurological symptoms including irritability, failure to thrive, apathy, anorexia and developmental regression which responds well to supplementation (Dror & Allen 2008).

Elderly

Vitamin B_{12} deficiency is common in the elderly, with estimates as high as 43% (Wolters et al 2004). Poor vitamin B_{12} status has been associated with vascular disease, depression, impaired cognitive performance and dementia. Elderly patients (> 60 years) should be monitored for evidence of B_{12} deficiency (a minimum threshold of 220–258 pmol/L (300–350 pg/mL) is desirable in the elderly) and general supplementation with vitamin B_{12} (> 50 μg/day) should be considered (Wolters et al 2004). Significantly higher doses may be required to correct deficiency. A randomised, parallel-group, double-blind, dose-finding trial found that the lowest dose of oral cyanocobalamin required to normalise mild vitamin B_{12} deficiency in the elderly is 647–1032 μg/day, more than 200-fold the recommended dietary allowance (Eussen et al 2005). Conversely another RCT reported that even low doses of B_{12} could improve the vitamin status in elderly people with food-bound vitamin B_{12} malabsorption. The dose required to increase mean serum vitamin B_{12} by 37 pmol/L was 5.9 μg/day (95% CI, 0.9–12.1) (Blacher et al 2007). In another study of elderly people with malabsorption taking 1000 μg/day of crystalline cyanocobalamin for 1 month, 85% of subjects normalised their serum cobalamin concentrations, and all subjects corrected their initial macrocytosis and had medullar regeneration with a mean increase in reticulocyte count (Andres et al 2006). While hearing loss has been associated with poor B_{12} status in the elderly, short term supplementation has so far failed to show benefits (Park et al 2006).

> ***Clinical note — Oral forms are effective***
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> Vitamin B_{12} is often given parenterally as an intramuscular injection, based on the understanding that oral doses will not be efficacious in cases of malabsorption.
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> There is now considerable evidence that oral vitamin B_{12} therapy is comparable in efficacy to parenteral therapy, even when intrinsic factor is not present or in other diseases affecting absorption (Andres et al 2005a, b, Bolaman et al 2003, Delpre et al 1999, Kuzminski et al 1998, Lederle 1991, Nyholm 2003, Oh & Brown 2003, Roth & Orija 2004, Vidal-Alaball et al 2005, Wellmer et al 2006). A 2005 Cochrane review suggests 2000 μg/day of oral vitamin B_{12} or 1000 μg initially daily then weekly and monthly may be as effective as intramuscular injections in obtaining short-term haematological and neurological responses in vitamin B_{12}-deficient patients (Vidal-Alaball et al 2005). As rare cases of anaphylaxis may occur with parenteral administration, oral therapy is also considered a safer option with improved cost and compliance (Bilwani et al 2005, Bolaman et al 2003). At doses of 500 μg/day correction of serum B_{12} levels is likely to occur within 1 week to 1 month, with correction of haematological abnormalities after at least 3 months (Andres et al 2005b).

Hyperhomocysteinaemia

Together with folic acid and vitamin B_6, vitamin B_{12} has been shown to reduce high plasma levels of homocysteine, which has been proposed as an independent risk factor for cardiovascular disease

(including atherosclerosis and coronary artery disease), cerebrovascular disease, peripheral vascular disease and venous thromboembolism (Clarke et al 1991, den Heijer et al 1996, Hung et al 2003, Lobo et al 1999, Malinow et al 1989, Selhub et al 1995), exudative ARMD, noise-induced hearing loss, cognitive dysfunction, and adverse pregnancy outcomes (Bjorke Monsen & Ueland 2003, Gok et al 2004, Nowak et al 2005).

Vitamin B_{12} alone may not be sufficient to normalise elevated homocysteine levels (Yajnik et al 2007). As a result, vitamin B_{12} is often recommended in combination with folic acid and vitamin B_6 in conditions for which homocysteine is implicated as a possible causative factor.

Cardiovascular protection

In practice, the relative safety and affordability of combined vitamin B supplementation (B_{12}, folic acid and B_6) make it an attractive recommendation in people with familial hyperhomocysteinaemia. Whether lowering total homocysteine improves cardiovascular mortality and morbidity is questionable as recent large scale clinical trials and meta-analyses have failed to demonstrate any benefits for either B_{12} alone or in combination for reducing overall cardiovascular risk, despite showing a reduction in homocysteine levels (Albert et al 2008, Clarke et al 2007, Mann et al 2008, Marcus et al 2007, Ray et al 2007). Failure of combined B vitamin therapy to reverse inflammatory processes associated with atherogenesis may partly explain the negative results (Bleie et al 2007). The consistent findings of an association between elevated plasma total homocysteine levels and vascular risk is yet to be fully explained, however it is possible that the association is a consequence rather than a cause of disease (Toole et al 2004).

Renal transplant recipients

Although studies investigating the effects of vitamin B_{12} as a stand-alone treatment in this condition are not available, several clinical studies have produced conflicting evidence for the use of combination vitamin B treatment (vitamin B_{12}, folic acid and B_6).

An RCT involving 56 renal transplant patients found that vitamin supplementation with folic acid (5 mg/day), vitamin B_6 (50 mg/day) and vitamin B_{12} (400 μg/day) for 6 months reduced the progression of atherosclerosis. Patients taking the vitamin combination experienced a significant decrease in homocysteine levels and carotid intima–media thickness, which is reflective of early atherosclerosis (Marcucci et al 2003). In a another trial, 36 stable renal transplant recipients with hyperhomocysteinaemia received a similar combination of 5 mg folic acid and 50 mg B_6, in addition to either 1000 μg B_{12} or placebo per day for 6 months. Supplementation decreased blood homocysteine and improved endothelium dependent and independent vasodilatation responses (Xu et al 2008). Despite these preliminary findings, combined therapy using even higher doses (40 mg folic acid, 100 mg B_6 and 2 mg B_{12}) did not improve survival (448 vitamin group deaths vs 436 placebo group deaths) (hazard ratio [HR], 1.04; 95% CI, 0.91–1.18) or reduce the incidence of vascular disease (MI, stroke and amputations) in patients with advanced chronic kidney disease or end-stage renal disease (Jamison et al 2007).

Restenosis after percutaneous coronary intervention

An RCT found that vitamin B_{12} (cyanocobalamin, 400 μg/day), folic acid (1 mg/day) and vitamin B_6 (pyridoxine hydrochloride, 10 mg/day) taken for 6 months significantly decreased the incidence of major adverse events including restenosis after percutaneous coronary intervention (Schnyder et al 2002).

Neural tube defects

Vitamin B_{12} is required to cleave folate, without which folate is not effective and postpartum analysis of serum B_{12} levels has shown an increased risk of NTD in women with low B_{12} status (Groenen et al 2004, Ray & Blom 2003, Suarez et al 2003). Some authors have called for combined fortification of food with folic acid and vitamin B_{12} because there are concerns about masking B_{12} deficiency (Czernichow et al 2005).

Noise-induced hearing loss

Homocysteine levels are significantly higher in subjects with noise-induced hearing loss as compared to healthy controls (Gok et al 2004) and elevated plasma B_{12} levels appear to play a protective role (Quaranta et al 2004).

Recurrent abortion

There appears to be a correlation between low serum B_{12} levels, increased homocysteine levels and early or very early recurrent abortion in some women (Reznikoff-Etievant et al 2002, Zetterberg et al 2002). One small study of five women with a history of very early recurrent abortion found that vitamin B_{12} supplementation resulted in four normal pregnancies (Reznikoff-Etievant et al 2002).

Depression

Elevation of homocysteine and low levels of vitamin B_{12} and folate are commonly seen in depression (Coppen & Bolander-Gouaille 2005). Observational studies have found as many as 30% of patients hospitalised for depression to be deficient in vitamin B_{12} (Hutto 1997). A recent cross-sectional study of 700 community-living, physically disabled women over the age of 65 years found that vitamin B_{12} deficient women were twice as likely to be severely depressed as non-deficient women (Penninx et al 2000). While studies using B_{12} alone could not be located, a prospective, double-blind, placebo-controlled study of 225 hospitalised acutely ill older patients receiving 400 mL of an oral nutritional supplement (106 subjects) or placebo (119 subjects) daily for 6 weeks reported significant increases in plasma vitamin B_{12} concentrations and red-cell folate, and a decrease in depression scores (Gariballa & Forster 2007).

Considering that symptoms of vitamin B_{12} deficiency can manifest as psychological disturbances such as depression, deficiency should be investigated in this population.

AIDS and HIV

Low vitamin B_{12} levels are often observed in patients infected with HIV type 1 (HIV-1) (Remacha & Cadafalch 1999, Remacha et al 1993). One study identified deficiency in 10–35% of all patients seropositive for HIV, presumably as a result of decreased intake, intestinal malabsorption and/or abnormalities in plasma binding proteins or antagonism by the drug azidothymidine. Importantly, as serum cobalamin levels declined, progression to AIDS increased and neurological symptoms worsened.

Cognitive impairment

Women in the highest quartile of plasma vitamin B_{12} levels during mid-life score significantly higher on cognitive function tests in later years and are cognitively equivalent to those 4 years younger (Kang & Grodstein 2005). Supplementation with vitamin B_{12} significantly reverses impaired mental function in individuals with pre-existing low levels (Healton et al 1991, Miller 2003, Refsum & Smith 2003, Tripathi et al 2001, Weir & Scott 1999). A complete recovery was observed in 61% of people with mental impairment due to low levels of vitamin B_{12}, according to one study (Healton et al 1991). It is unclear whether vitamin B_{12} (and folate) deficiency exacerbates a pre-existing but undiagnosed pathological condition or whether it may cause cognitive decline even in normal subjects (Moretti et al 2004).

Prevention when with elevated homocysteine

Hyperhomocysteinaemia has been shown to be an independent risk factor for cognitive dysfunction, as both indirect and direct vascular damage can be caused by homocysteine. It has also been implicated in vascular dementia, with an increased risk of multiple brain infarcts and dementia as homocysteine levels rise. As a result, the homocysteine-lowering action of vitamin B_{12} provides a theoretical basis for its use in these cases. However, a trial using 1000 μg B_{12} alone or in combination with 400 μg folic acid failed to demonstrate a significant improvement in cognitive performance (Eussen et al 2007) and this is consistent with other research in this field (Eussen et al 2006, McMahon et al 2006). Similarly, a systematic review of B_{12}, B_6 and folic acid (alone or in combination) found insufficient evidence to suggest benefits on cognitive function testing in people with either normal or impaired cognitive function (Balk et al 2007).

One study of 370 non-demented 75-year-olds found a twofold increased risk of developing Alzheimer's dementia in subjects with low serum levels of vitamin B_{12} and folate over a 3-year period (Wang et al 2001).

In a study involving 30 mild to moderate dementia patients with vitamin B_{12} deficiency, B_{12} therapy reduced Delirium Rating Scale scores associated with dementia but did not result in significant changes in cognitive function or behavioural symptoms. The B_{12} therapy involved 3 intramuscular injections of methylcobalamin (1 mg) in the first week, oral supplementation with methylcobalamin (1 tablet 3 times a day) for 16 weeks, and 1 intramuscular injection of cyanocobalamin (1 mg) once a month for 6 months (Kwok et al 2008).

Diabetic neuropathy

According to a recent review of seven RCTs, vitamin B_{12} supplementation may improve pain and paraesthaesia in patients with diabetic neuropathy (Sun et al 2005). The studies cited, however, were generally of low quality and more research is required to confirm these results and determine whether positive effects are due to the correction of deficiency or to alteration of abnormal metabolism.

Sleep disorders

A preliminary study investigated the effects of randomly assigned methyl- and cyanocobalamin on circadian rhythms, wellbeing, alertness and concentration after 14 days in 20 healthy subjects (Mayer et al 1996). Methylcobalamin supplementation led to a significant decrease in daytime melatonin levels, improved sleep quality, shorter sleep cycles, increased feelings of alertness, better concentration, and a feeling of waking up refreshed in the morning. It appeared that methylcobalamin was significantly more effective than cobalamin.

Tinnitus

A group of 113 army personnel (mean age 39 years) exposed to military noise was studied, of which 57 had chronic tinnitus and noise-induced hearing loss (Shemesh et al 1993). Of this subset, 47% also had vitamin B_{12} deficiency. Treatment with vitamin B_{12} supplementation produced some improvement in tinnitus and associated symptoms.

OTHER USES

Human trials have shown vitamin B_{12} levels to be low in people with recurrent aphthous stomatitis, suggesting a possible aetiological factor (Piskin et al 2002). An inhalation of vitamin B_{12} mixed solution has been shown to be effective for the treatment of acute radiation-induced mucosal injury (Chen & Shi 2006).

Erythema nodosum

A case report exists of a 38-year-old female diagnosed with erythema nodosum and B_{12} deficiency whose symptoms resolved completely without re-occurrence following vitamin B_{12} therapy (Volkov et al 2005). Testing for deficiency may be advised in such cases.

Atopic dermatitis

A novel use for B_{12} in a topical cream for atopic dermatitis has recently been tested. A prospective, randomised, placebo-controlled phase III multicentre trial involving 49 patients was conducted. Subjects applied the B_{12} cream twice daily to one side of the body and a placebo cream to the contralateral side, according to the randomisation scheme, for

8 weeks. The B_{12} cream was reported to significantly improve the extent and severity of atopic dermatitis and was considered safe and very well tolerated (Stucker et al 2004).

Multiple sclerosis

Multiple sclerosis (MS) and vitamin B_{12} deficiency share common inflammatory and neurodegenerative characteristics and low or decreased levels of vitamin B_{12} have been demonstrated in MS patients and may correlate with early onset (<18 years) (Miller et al 2005). Considering vitamin B_{12} is a cofactor, and myelin formation has important immunomodulatory and neurotrophic effects (Loder et al 2002, Miller et al 2005, Sandyk & Awerbuch 1993), a theoretical basis exists for its use in MS.

Amyotrophic lateral sclerosis (ALS)

Early evidence suggests a possible benefit for long-term ultra-high-dose methylcobalamin (administered IV or IM) for sporadic or familial cases of ALS (Izumi & Kaji 2007), however large-scale clinical trials are required to assess the efficacy and safety of this treatment.

DOSAGE RANGE

Australian RDI

- Adult >13 years: 2.4 μg/day.
- Pregnancy: 2.6 μg/day.
- Lactation: 2.8 μg/day.

Requirements may be higher for elderly people with impaired digestion or absorption.

- Sublingual cyanocobalamin: 1000–2000 μg/day taken 30 minutes before breakfast.
- Pernicious anaemia: generally, vitamin B_{12} 1000 μg IM 2–4 times weekly is given until haematological abnormalities are corrected, and then it is given once monthly. Alternatively, oral B_{12} can be given in very large doses (0.5–2 mg/day). Correction of haematological abnormalities usually occurs within 6 weeks of treatment, but neural improvement may take up to 18 months.
- Homocysteine lowering: 0.5 mg/day (Dusitanond et al 2005).

Note: Sublingual cobalamin is the preferred oral form for many practitioners with methylcobalamin also becoming available in some regions.

ADVERSE REACTIONS

Although adverse effects to parenteral cobalamin have been reported, oral supplements appear to be well tolerated (Hillman 1996, Branco-Ferreira et al 1997).

SIGNIFICANT INTERACTIONS

Carbamazepine

In studies with children, long-term carbamazepine use led to a decrease in vitamin B_{12} levels (Karabiber et al 2003) — observe for signs and symptoms of B_{12} deficiency. Increased intake may be required with long-term therapy.

Gastric acid inhibitors: PPI and H2 receptor antagonists

Gastric acid is required to liberate protein-bound cobalamin. Therefore, vitamin B_{12} concentration may be decreased when gastric acid is markedly suppressed for prolonged periods (Laine et al 2000, Schenk et al 1999, Termanini et al 1998). Studies have shown that omeprazole therapy acutely decreases cyanocobalamin absorption in a dose-dependent manner (Marcuard et al 1994, Saltzman et al 1994) and deficiency may occur with long-term use (Valuck & Ruscin 2004). It should be noted that vitamin B_{12} supplements do not suffer the same fate, as they are not bound to protein — observe for signs and symptoms of B_{12} deficiency; vitamin B_{12} supplements may be required with long-term therapy.

Hydrochlorothiazide

There are a number of medications that have the ability to increase homocysteine levels, such as hydrochlorothiazide (Westphal et al 2003), therefore concurrent use of vitamin B_{12} (with folic acid) may be a useful adjunct — potential beneficial interaction.

Lithium

Lithium administration may result in a decrease in serum B_{12} concentration; however, the clinical significance of these findings is not yet clear (Cervantes 1999). Beneficial interaction is possible.

Metformin

In patients with type 2 diabetes, metformin has been shown to reduce levels of vitamin B_{12} (and folate) and increase homocysteine (Sahin et al 2007). This effect was not demonstrated in women with polycystic ovary syndrome taking metformin and receiving vitamin B_{12} and folate substitution, a daily oral multivitamin tablet, and dietary and lifestyle advice (Carlsen et al 2007). Supplementation may be beneficial.

Oral contraceptive pill

Users of the OCP showed significantly lower concentrations of cobalamin than controls in a 2003 clinical study (Sutterlin et al 2003). However, it would appear that this may be due to an effect on B_{12} binding proteins in serum affecting test results, because total homocysteine and methylmalonic acid markers were unchanged and no symptoms of deficiency were present (Bor 2004) — observe for signs and symptoms of B_{12} deficiency and conduct testing if deficiency is suspected.

Phenobarbital and phenytoin

One clinical study reports that combined long-term use of phenobarbital and phenytoin resulted in significantly increased serum levels of vitamin B_{12} (Dastur & Dave 1987) — observe patients taking this combination.

Prednisolone

Decreased vitamin B_{12} levels have been reported in the cerebrospinal fluid and serum of multiple sclerosis patients following high-dose (1000 mg daily for

PRACTICE POINTS/PATIENT COUNSELLING

- Vitamin B_{12} (cobalamin) is a water-soluble vitamin obtained mostly from animal protein products in the diet.
- There is considerable evidence that oral vitamin B_{12} therapy is comparable in efficacy to parenteral therapy, even when intrinsic factor is not present or in other diseases affecting absorption.
- As numerous studies have indicated that serum B_{12} levels are an inadequate guide to B_{12} status, a combination of total homocysteine and methylmalonic acid is probably the clearest indicator.
- Vitamin B_{12} deficiencies manifest primarily as haematological and neurological disturbances and is estimated to affect 10–15% of individuals over the age of 60 years.
- Traditionally, supplementation is recommended to treat deficiency states or prevent them in people at risk such as in pernicious anaemia or atrophic gastritis.
- When administered together with folic acid and vitamin B_6 (pyridoxine), it is used to reduce homocysteine levels. In this way, vitamin B_{12} is sometimes recommended in conditions where homocysteine is implicated as a possible causative factor.
- Some evidence has shown supplementation can be useful in HIV and AIDS, depression, tinnitus and cognitive impairment when low vitamin B_{12} levels are also present. Preliminary evidence also suggests a possible role for supplementation in diabetic retinopathy and sleep disturbances.
- There are several commonly prescribed pharmaceutical medicines that can reduce vitamin B_{12} absorption when used long term.

10 days) intravenous methylprednisolone (Frequin et al 1993). Given the suggested importance of B_{12} in MS sufferers, a beneficial interaction is possible.

Tetracycline antibiotics

B complexes containing B_{12} may significantly reduce the bioavailability of tetracycline hydrochloride (Omray 1981) — separate doses by at least 2 hours.

CONTRAINDICATIONS AND PRECAUTIONS

- Parenteral cyanocobalamin given for vitamin B_{12} deficiency caused by malabsorption should be given intramuscularly or by the deep subcutaneous route but never intravenously.
- Folic acid supplementation may mask a B_{12} deficiency.
- Treatment with cyanocobalamin should be avoided in cases of altered cobalamin metabolism or deficiency associated with chronic cyanide intoxication (Freeman et al 1999).

PREGNANCY USE

Vitamin B_{12} is considered safe in pregnancy.

Low-dose vitamin B_{12} (1–18 μg/day) does not appear to impact on the circulating level of serum cobalamins or its binding proteins in lactating women (Morkbak et al 2007). If required, higher doses may need to be utilised.

PATIENTS' FAQs

What will this vitamin do for me?

Vitamin B_{12} is essential for healthy growth, development and health maintenance. It will reverse signs and symptoms of deficiency and can alleviate symptoms of tinnitus, poor memory, depression and HIV and AIDS when low vitamin B_{12} levels are also present. There is also some research suggesting some positive effects in diabetic retinopathy and sleep disturbances.

When will it start to work?

In cases of pernicious anaemia, the classical deficiency state, correction of blood abnormalities occurs within 6 weeks; however, correction of nervous system changes is slower and may take up to 18 months.

Are there any safety issues?

Vitamin B_{12} is considered a very safe nutrient.

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Vitamin C

HISTORICAL NOTE Vitamin C deficiency has been known for many centuries as scurvy, a potentially fatal condition, dreaded by seamen in the 15th century, who were often forced to subsist for months on diets of dried beef and biscuits. It was also described by the European crusaders during their numerous sieges. In the mid-1700s Lind was the first doctor to conduct systematic clinical trials of potential cures for scurvy, identifying oranges and lemons as successful treatments (Bartholomew 2002). However, it was not until 1928 that vitamin C (then known as antiscorbutic factor) was isolated, leading to mass production in the mid-1930s.

BACKGROUND AND RELEVANT PHARMACOKINETICS

Vitamin C is an essential nutrient for humans and required in the diet on a regular basis, as we are one of few species of animals that cannot synthesise it. This is because humans lack the enzyme L-gulonolactone oxidase, which is required for the conversion of glucose into vitamin C (Braunwald et al 2003).

The bioavailability of ascorbic acid is dependent on both intestinal absorption and renal excretion. Vitamin C, consumed either in the diet or as dietary supplements, is absorbed by the epithelial cells of the small intestine by the sodium vitamin C co-transporter 1 (SVCT1) and subsequently diffuses into the surrounding capillaries and then passes into the circulatory system (Li & Schellhorn 2007). Ultimately, the degree of absorption depends on the dose ingested and decreases as the dose increases. This is because at low concentrations, most vitamin C is absorbed in the small intestine and reabsorbed from the renal tubule, but at high concentrations SVCT1 becomes saturated, which, combined with ascorbate-mediated SVCT1 down-regulation, limits the amount of ascorbic acid absorbed from the intestine and reabsorbed from the kidney (Li & Schellhorn 2007). For this reason, oral vitamin C is best absorbed when it is ingested in small doses at regular intervals. Complete plasmatic saturation occurs at 1000 mg daily with a concentration of around 100 μM (Verrax et al 2008). Pectin and zinc are also able to impair oral absorption. These limitations are bypassed with the use of intravenously administered vitamin C, which can achieve much higher plasma levels than oral administration.

Following its absorption, ascorbic acid is ubiquitously distributed in the cells of the body. Within the body, the highest levels of ascorbic acid are found in the adrenal glands, the white blood cells, skeletal muscles and the brain, especially in the pituitary gland (Verrax et al 2008). Interestingly, the brain is the most difficult organ to deplete of ascorbate. As a polar compound with a relatively large molecular weight, vitamin C cannot readily cross the cell membrane by simple diffusion. The flux of vitamin C in and out of the cell is controlled by specific mechanisms, including facilitated diffusion and active transport, which are mediated by distinct classes of membrane proteins such as facilitative glucose transporters (GLUT) and sodium vitamin C co-transporters (SVCT) respectively (Li & Schellhorn 2007). Once in cells, dehydroascorbic acid (the oxidised form of ascorbate) is rapidly reduced to ascorbate (Harrison & May 2009). Eventually it is metabolised in the liver, filtered by the kidneys, and excreted in the urine. The biological half-life of vitamin C is 8–40 days (NHMRC 2006).

Clinical note — Differences between major forms of vitamin C supplement

Here is a brief summary of the most common forms found in OTC supplements.

- *Ascorbic acid*. The major dietary form of vitamin C.
- *Mineral ascorbates* (also known as non-acid vitamin C). These are buffered forms of vitamin C and believed to be less irritating to the stomach than ascorbic acid. Sodium ascorbate and calcium ascorbate are the most common forms. When mineral salts are taken, both the ascorbic acid and the mineral are absorbed. For example, sodium ascorbate generally provides 131 mg of sodium per 1000 mg of ascorbic acid, and calcium ascorbate provides 114 mg of calcium per 1000 mg of ascorbic acid.
- *Vitamin C with bioflavonoids*. Many bioflavonoids are antioxidant substances and are added to some vitamin C preparations in the belief that this increases the bioavailability or efficacy of vitamin C. Typically, the bioflavonoids are sourced from citrus fruits.
- *Ascorbyl palmitate*. A fat-soluble form of vitamin C formed by esterification with palmitic acid and most often used in topical creams.

CHEMICAL COMPONENTS

Vitamin C exists as both its reduced form (L-ascorbic acid) and its oxidised form (L-dehydroascorbic acid). The two forms interchange in the body in a reversible equilibrium.

FOOD SOURCES

Vitamin C is found in many different fruits and vegetables. The most concentrated food sources are blackcurrants, sweet green and red peppers, hot red peppers, green chilli peppers, oranges and its fresh juice, and strawberries. Other good sources are watermelon, papaya, citrus fruits, cantaloupe, mango, cabbage, cauliflower, broccoli and tomato juice. In practice, vegetables may be a more important source of vitamin C than fruits because they are often available for longer periods during the year.

The vitamin C content of food is strongly influenced by many factors, such as season, transportation, shelf life, storage conditions and storage time, cooking techniques and chlorination of water (FAO/WHO 2002). Cutting or bruising food will reduce its vitamin C content; however, blanching or storing at low pH will preserve it.

Up to 100% of the vitamin C content of food can be destroyed during cooking and storing because the vitamin is sensitive to light, heat, oxygen and alkali (Wahlqvist 2002). Additionally, using too much water during cooking can leach the vitamin from food and further reduce its vitamin C content.

DEFICIENCY SIGNS AND SYMPTOMS

In adults, scurvy remains latent for 3–6 months after reducing dietary intake to less than 10 mg/day (Beers & Berkow 2003). It manifests when the body pools fall below 300–400 mg (NHMRC 2006). Many of the features of frank vitamin C deficiency (scurvy) result from a defect in collagen synthesis.

Early symptoms are:

- weakness
- fatigue and listlessness
- muscular weakness
- petechial haemorrhages and ecchymoses (bruising)
- swollen gums
- poor wound healing and the breakdown of recently healed wounds
- poor appetite and weight loss
- emotional changes such as irritability and depression
- vague myalgias and arthralgias
- congested hair follicles.

Symptoms of more severe deficiency are:

- fever
- drying of the skin and mucous membranes
- susceptibility to infection
- bleeding gums and loosening of teeth
- oedema of the lower extremities
- anaemia
- joint swelling and tenderness, due to bleeding around or into the joint
- oliguria
- pain in the extremities
- haemorrhage
- convulsions
- shock
- eventually death if left untreated.

Clinical note — Deficiencies in smokers

It is well established that smokers have lowered vitamin C status than non-smokers and therefore have higher requirements for vitamin C. Vitamin C status is inversely related to cigarette use (Cross & Halliwell 1993). The depletion of plasma ascorbic acid associated with cigarette smoking was first described in the late 1930s. Reports have shown that low ascorbic acid concentrations in the plasma, leukocytes and urine of both male and female cigarette smokers are associated with increased numbers and activity of neutrophils, which suggests increased utilisation and lower intake, or reduced bioavailability of vitamin C in smokers than in non-smokers (Northrop-Clewes & Thurnham 2007).

Although frank deficiency is uncommon in Western countries, marginal deficiency states are not uncommon.

Primary deficiency

This occurs if there is an inadequate dietary intake, which is often caused by a combination of poor cooking and eating habits. It occurs in areas of urban poverty, during famine and war, in young children fed exclusively on cow's milk for a prolonged period, in the institutionalised or isolated elderly, and in chronic alcoholics (Pimentel 2003, Richardson et al 2002). One Australian hospital identified that 73% of all new admissions had hypovitaminosis C and 30% had levels suggestive of scurvy (Richardson et al 2002).

Secondary deficiency

Factors that increase nutritional requirements include cigarette smoking, pregnancy, lactation, thyrotoxicosis, acute and chronic inflammatory diseases, major surgery and burns, infection and diabetes (Beers & Berkow 2003, FAO/WHO 2002, Hendler & Rorvik 2001, Wahlqvist 2002). Decreased vitamin C absorption in achlorhydria and increased excretion in chronic diarrhoea also increase the risk of deficiency, particularly when combined with poor dietary intake.

MAIN ACTIONS

Vitamin C is an electron donor (reducing agent or antioxidant), and this accounts for most of its biochemical and molecular functions. It is involved in many biochemical processes in the body such as:

- energy release from fatty acids
- metabolism of cholesterol
- reduction of nitrosamine formation in the stomach
- formation of thyroid hormone
- carnitine biosynthesis
- modulation of iron and copper absorption
- corticosteroid biosynthesis
- protection of folic acid reductase, which converts folic acid to folinic acid
- collagen biosynthesis
- tyrosine biosynthesis and catabolism
- neurotransmitter biosynthesis.

The main actions of vitamin C are summarised below.

Antioxidant and pro-oxidant

At physiological concentrations, vitamin C is one of the most important water-soluble antioxidant substances in the body, acting as a potent free-radical scavenger in the plasma, protecting cells against oxidative damage caused by reactive oxygen species (ROS). It scavenges free-radical oxygen and nitrogen species such as superoxide, hydroxyl, peroxyl and nitroxide radicals and non-radical reactive species such as singlet oxygen, peroxynitrite and hypochlorite (FAO/WHO 2002, Hendler & Rorvik 2001). Besides having a direct antioxidant function, it also indirectly increases free-radical scavenging by regenerating vitamin E (Vatassery 1987) and maintaining glutathione in reduced form. Much of the vitamin's physiological role stems from its very strong reducing power (high redox potential) and its ability to be regenerated using intracellular reductants such as glutathione, nicotinamide adenine dinucleotide and nicotinamide adenine dinucleotide phosphate (Chaudière & Ferrari-Iliou 1999).

Paradoxically, ascorbic acid may also function as a pro-oxidant, promoting oxidative damage to DNA in the presence of free transition metals such as copper and iron, which are reduced by ascorbate and, in turn, react with hydrogen peroxide, leading to the formation of highly reactive and damaging hydroxyl radicals. The effect does not appear to be significant under normal physiological conditions in vivo; however, when used at higher pharmacological concentrations (0.3–20 mmol/L), ascorbic acid displays transition metal-independent pro-oxidant activity, which is more profound in cancer cells than healthy cells and causes cell death (Li & Schellhorn 2007).

Whether vitamin C functions as an antioxidant or pro-oxidant is determined by at least three factors: (1) the redox potential of the cellular environment, (2) the presence/absence of transition metals and (3) the local concentrations of ascorbate (Li & Schellhorn 2007).

Maintenance of connective tissue

Vitamin C maintains the body's connective tissue and is essential for the formation of collagen, the major fibrous element of blood vessels, skin, tendon, cartilage and teeth (Morton et al 2001). If collagen is produced in the absence of vitamin C, it is unstable and cannot form the triple helix required for normal tissue structure. Vitamin C is involved in the biosynthesis of other substances important for connective tissue, such as elastin, proteoglycans, bone matrix, fibronectin and elastin-associated fibrillin (Hall & Greendale 1998).

These effects have been harnessed by the dermatological and cosmetic industries and are the rationale for producing topically applied products containing vitamin C.

Brain and nerve function

Ascorbate is involved in neurotransmitter synthesis. It is a cofactor required for the biosynthesis of noradrenaline from dopamine and hydroxylation of tryptophan to produce serotonin. It also acts as a modulator of glutaminergic, cholinergic and GABAergic transmission (Bornstein et al 2003, FAO/WHO 2002, Harrison & May 2009). Furthermore, it is involved in neural maturation and acts as a neuroprotective agent (Harrison & May 2009),

Immunostimulant

Both in vivo and in vitro studies provide evidence of immunostimulant effects, generally at doses beyond RDI levels. Vitamin C favourably modulates lymphocytes and phagocytes, regulates NK cells and can influence antibody and cytokine synthesis under certain situations (Hendler & Rorvik 2001). In high doses, it is a potent immunomodulator and is preferentially cytotoxic to neoplastic cells. Vitamin C enhances the activity of NK cells in vivo and also both B- and T-cell activity (Drisko et al 2003).

Antihistamine

An inverse association has been identified between blood histamine levels and vitamin C status in humans (Johnston et al 1996). In that study, increasing vitamin C status with supplements (up to 250 mg/day) over 3 weeks was shown to decrease histamine levels. It is unclear whether single, high-dose supplementation also affects histamine levels, as two studies using 2 g doses have produced conflicting results (Bucca et al 1990, Johnston et al 1992).

Anticancer

In millimolar concentrations, vitamin C is selectively cytotoxic to many cancer cell lines and has in vivo anticancer activity when administered alone or together with other agents (Hoffer et al 2008). Importantly, pharmacological concentrations of ascorbic acid (0.3–20 mmol/L) are required to find evidence of cytotoxicity in vitro and in vivo, whereas physiological concentrations of ascorbic acid (0.1 mmol/L) do not have any effect on either tumour or normal cells (Li & Schellhorn 2007). The most reliable method of achieving these high doses is with IV administration of vitamin C and not via the oral route, which has limited absorption (Padayatty et al 2006). The effect is clearly dose-dependent and mediated via several mechanisms, such as immunomodulation, inhibition of cell division and growth, gene regulation and induction of apoptosis. One mechanism of cytotoxicity demonstrated in several models is the ability of ascorbate at pharmacological concentrations to exert pro-oxidant activity, generating hydrogen-peroxide-dependent cytotoxicity towards a variety of cancer cells in vitro and in vivo without adversely affecting normal cells (Chen et al 2008, Tamayo & Richardson 2003).

Much investigation has been undertaken to understand how preferential cytotoxicity is achieved; however, the mechanisms are still largely unknown. For example, studies with radioactive-labelled vitamin C have found that tumour cells accumulate more vitamin C than healthy cells, whereas other studies have reported no differences in intracellular concentrations (Prasad et al 2002). There is also some preliminary evidence of

synergistic cytotoxic effects and decreased drug toxicity with some pharmaceutical anticancer agents (Giri et al 1998).

One theory proposed to explain the preferential targeting of tumour cells relates to their overexpression of facilitative glucose transporters (GLUTs) (Gatenby & Gillies 2004) and dehydroascorbic acid, transported by GLUTs, accumulating within the tumour cells, which enables intracellular hydrogen peroxide levels to increase (Verrax et al 2008, Chen et al 2005, Zhang et al 2001). Other intrinsic properties of cancer cells may also be involved, such as reduced concentrations of antioxidant enzymes (e.g. catalase and superoxide dismutase) and increased intracellular transitional metal availability, both of which further augment free-radical production (Li & Schellhorn 2007). Alternatively, it has been suggested that extracellular ascorbate is the source of this anti-cancer effect and is more important than intracellular vitamin C.

Ascorbyl stearate is a lipophilic, vitamin C derivative that has also demonstrated antitumorigenic properties in vitro (Fang et al 2006).

Modulation of gene expression

Many transcription factors, such as NF-jB, AP-1 or PPARs, are redox regulated, and moderate amounts of oxidative stress are known both to modulate gene expression and to signal transduction cascades by affecting kinases, phosphatases as well as Ca^{2+} signalling. L-ascorbic acid may modulate relatively unspecific gene expression by affecting the redox state of transcription factors and of enzymes involved in signal transduction (see Table 1).

OTHER ACTIONS

High oral doses (4–12 g/day in divided doses) can acidify urine.

CLINICAL USE

Vitamin C is an important biological antioxidant and has been a popular nutritional supplement for decades. It is administered as intramuscular or intravenous injections and used topically and orally. This review will chiefly focus on oral and topical use, as these are the forms of vitamin C most commonly used by the public.

TABLE 1 Known or Putative Genes and Enzymatic Activities Responsive to L-Ascorbic Acid (Adapted from Villacorta et al 2007)

Gene	Cellular process involved	Mechanism	Expression/activity with L-ascorbic acid
h1-Calponin	VSMC phenotypic modulation	?	↑
h-Caldesmon	VSMC phenotypic modulation	?	↑
SM22α	VSMC phenotypic modulation	?	↑
α-SM actin	VSMC phenotypic modulation	?	↑
Collagen I	Matrix production	Transcription, mRNA stability	↑
Collagen III	Matrix production	Transcription, mRNA stability	↑
Elastin	Elasticity of arterial wall, VSMC phenotypic modulation	mRNA stability	↓
MMP2	Matrix degradation	?	↓
TIMP1	Inhibits matrix degradation	?	↑
Calponin 1	VSMC phenotypic modulation	?	↑
Myosin heavy chain-1	VSMC phenotypic modulation	?	↑
GATA4	Cardiac development	?	↑
Nkx2.5	Cardiac development	?	↑
ANF	Regulation of cardiac and vascular tone	?	↑
eNOS	Vascular homeostasis	Increased intracellular Ca^{2+}	↑
Prolyl hydroxylase	Stability and secretion of collagen	Co-factor	↑
ICAM-1	Cell adhesion	?	↓
Enzymes involved in carnitine synthesis	Fatty acid metabolism	Co-factor (epsilon-*N*-trimethyllysine hydroxylase and gamma-butyrobetaine hydroxylase)	↑

As with many nutrients, studies associating dietary vitamin intake and disease risk are difficult to interpret. This is because it is difficult to separate the effects of the individual vitamin from the effects of other components in the diet. Where possible, an effort has been made to include information that will help in the interpretation of this type of data.

Deficiency: prevention and treatment

Traditionally, vitamin C supplements are used both to treat and to prevent deficiency. Treatment may include 250 mg vitamin C daily and encouragement to eat fresh fruits and vegetables on a regular basis (Kumar et al 2002), or 100 mg taken 3–5 times daily until 4000 mg has been reached (Braunwald et al 2003). Some deficiency symptoms start to respond within 24 hours, although most take from several weeks to months to resolve completely.

Iron-deficiency anaemia

Ascorbic acid is considered a potent enhancer of iron absorption. Vitamin C facilitates iron absorption by forming soluble complexes and may be used with an iron supplement and nutritious diet in the treatment of iron-deficiency anaemia. It is also recommended for women with menorrhagia in order to reduce the risk of iron deficiency.

Upper respiratory tract infections (URTIs)

Vitamin C is widely used both to prevent and to treat common URTIs, such as the common cold and influenza, largely based on its effects on the immune system, its ability to reduce histamine levels, and the observations that the gastrointestinal absorption of vitamin C increases in the common cold (suggesting an increased demand for this nutrient) and that vitamin C concentrations in the plasma and leucocytes rapidly decline during infection (Wilson et al 1976, Wintergerst et al 2006). Although extremely popular, its usefulness in these conditions is widely debated.

A 2004 Cochrane Review of 29 placebo-controlled studies involving 11,077 participants found that regular ingestion of vitamin C in doses of 200 mg did not reduce the incidence of the common cold in the normal population; however, a subgroup of six trials that involved a total of 642 marathon runners, skiers and soldiers on subarctic exercises did find significant protective effects (Douglas et al 2004). Data from 9676 respiratory episodes suggested that regular vitamin C supplementation was consistently associated with a small reduction in the duration and severity of common cold symptoms; however, the magnitude of the effect was described as small. When high doses of vitamin C have been started after the onset of cold symptoms, there has been no consistent effect on either the duration or the severity of symptoms. Equivocal results were obtained in one large trial that used a dose of 8 g at the onset of symptoms, whereas two trials using supplementation for 5 days did report a benefit.

Since then, a long-term study reported that use of 500 mg/day vitamin C significantly reduced the risk of the common cold (relative risk 0.34), although no reduction in severity or duration was seen (Sasazuki et al 2006). The double-blind RCT was conducted over 5 years and, due to protocol amendment, these results should be viewed conservatively.

There are a number of factors that may be contributing to the inconsistent results obtained to date, such as the variable characteristics of the subjects studied, type of infecting virus, lack of control for dietary vitamin C intake and differences in measures of outcomes. Clearly, further investigation is required to clarify many issues surrounding the use of vitamin C supplements for URTIs. In practice, naturopaths often recommend megadoses of vitamin C (taken frequently, in small amounts), which are well beyond the doses investigated so far, and often report good results. Although anecdotal, it is interesting to note that little research has investigated this method.

Dermatological uses

Vitamin C is used as an oral supplement or topical application in a number of dermatological conditions.

Wound healing

Vitamin C is important for effective wound healing, as deficiency contributes to fragile granulation tissue and therefore impairs the wound-healing process (Russell 2001).

In vitro studies with skin graft samples have demonstrated that vitamin C extends cellular viability, promotes formation of an epidermal barrier and promotes engraftment (Boyce et al 2002). In this way, vitamin C is used to enhance wound healing before surgery has commenced.

Numerous case reports of surgical and dental patients generally suggest a use for vitamin C supplementation in doses beyond RDI as a means of enhancing the rate of wound healing (Ringsdorf & Cheraskin 1982). One early double-blind study found that vitamin C (500 mg twice daily) resulted in a significant mean reduction in pressure-sore area of 84% after 1 month compared with 43% in the placebo group (Taylor et al 1974). The mean rates of healing were 2.47 cm^2 for vitamin C and 1.45 cm^2 for the placebo.

Photo-damaged skin

Two double-blind studies investigating the effects of topical preparations of vitamin C on photo-damaged skin have demonstrated good results after 3 months' use (Fitzpatrick & Rostan 2002, Humbert et al 2003). One study tested a topical application of 5% vitamin C in a cream base, whereas the other used a newly formulated vitamin C complex having 10% ascorbic acid (water-soluble) and 7% tetrahexyldecyl ascorbate (lipid-soluble) in an anhydrous polysilicone gel base.

Prevention of sunburn

One controlled study found oral vitamin C (2000 mg/day) in combination with vitamin E (1000 IU/day) had a protective effect against sunburn after 8 days' treatment in human subjects (Eberlein-Konig et al 1998).

Similar results have been obtained for topical vitamin C preparations in several animal models (Darr et al 1992, 1996, Lin JY et al 2003) and a small human study (Keller & Fenske 1998). The latter found that application of an aqueous 10% L-ascorbic acid solution after UVB radiation produced a significant reduction in the minimal erythema dose and a less intense erythematous response than controls.

Reduction in all-cause mortality

Several studies have identified an inverse association between plasma ascorbate levels, vitamin C intake and all-cause mortality.

In the Western Electric Company Study, data on diet and other factors were obtained in 1958 and 1959 for a cohort of 1556 employed middle-aged men and an inverse association between vitamin C and mortality was identified (Pandey et al 1995). The next year, a prospective cohort study conducted with 725 older adults also identified an inverse relationship between vitamin C blood concentrations and total mortality during a 12-year follow-up (Sahyoun et al 1996). Similar results were obtained in the large EPIC-Norfolk study of 19,496 men and women aged 45–79 years (Khaw et al 2001). Plasma ascorbate concentration was inversely related to mortality from all causes, and from cardiovascular disease and ischaemic heart disease in both men and women. Risk of mortality in the group with the highest intake was about half that of the low intake group and was independent of age, systolic blood pressure (SBP), serum cholesterol, cigarette smoking, diabetes or supplement use.

The Second National Health and Nutrition Examination Survey (NHANES II) Mortality Study further confirmed the inverse association between plasma ascorbate and risk of dying from all causes; however, this study identified a gender difference (Loria et al 2000). After adjustments for race, educational level, number of cigarettes smoked at baseline, serum total cholesterol, SBP, body mass index, diabetes status and alcohol consumption, men in the lowest serum ascorbate quartile (serum ascorbate concentrations < 28.4 micromol/L) had a 57% higher risk of dying from any cause than did men in the highest quartile (> 73.8 micromol/L). Additionally, men in the lowest serum ascorbate quartile had double the risk of dying from cancer than those in the highest quartile after adjustment for age. The dose corresponds to approximately 60 mg/day vitamin C. In contrast, among women no association was observed between quartiles of serum ascorbate concentration and total mortality or mortality from cardiovascular disease or cancer.

A gender difference was also reported in the NHANES I Epidemiologic Follow-up Study (NHEFS) (Enstrom et al 1992). Vitamin C intakes > 50 mg/day plus regular supplement use were associated with reduced mortality, compared with intakes < 50 mg/day in men, but apparently not in women.

Prevention of cardiovascular disease

The association between vitamin C and cardiovascular disease prevention is still unclear, although several themes are emerging as evidence accumulates. In general, laboratory, epidemiological and observational follow-up studies suggest that vitamin C is associated with reduced incidence of cardiovascular disease, although not all studies are positive (Houston 2005). Studies have looked at blood levels, dietary intake and supplemental vitamin C; in some studies, vitamin C is co-administered with other nutrients (often vitamin E), making it difficult to assess the contribution of vitamin C alone (Carr & Frei 1999, Khaw et al 2001, Knekt et al 2004, Kushi et al 1996, Lopes et al 1998, MRC/BHF 2002, Ness et al 1996, Nyyssonen et al 1997, Osganian et al 2003). Apart from these and other well-recognised confounding phenomena, the inconsistency is due at least in part to our limited understanding of the mechanisms of action of this vitamin on different pathophysiological variables contributing to cardiovascular complications; as such, more focused mechanistic studies on the interaction of ascorbic acid with contributors of specific vascular pathology are required (Li & Schellhorn 2007). Overall, it appears that if a protective effect is observed with supplementation, it is most likely with doses above RDI and long-term use, and in populations with a substantial proportion of people who have low or deficient intakes of vitamin C.

Possible mechanisms

According to a 2001 review, ascorbic acid is inversely related to several risk factors and indicators of atherosclerotic cardiovascular disease, including hypertension and elevated concentrations of LDL, acute phase proteins and haemostatic factors (Price et al 2001). More specifically, vitamin C inhibits oxidative modification of LDL cholesterol directly through free-radical scavenging activity according to in vitro data, and indirectly by increasing glutathione and vitamin E concentrations within cell membranes. This has been demonstrated against the pro-oxidant combination of homocysteine and iron (Alul et al 2003) and may have implications for other diseases such as Alzheimer's dementia.

More recently, evidence suggests that other mechanisms are also likely to be involved. Vitamin C is linked to endothelial function and glucose metabolism. It improves endothelial dysfunction in smokers, renal transplant recipients, patients with cardiovascular disease after a fatty meal, people with intermittent claudication diabetes and those with hypertension (Kaufmann et al 2000, Ling et al 2002, Silvestro et al 2002, Solzbach et al 1997, Williams et al 2001), but not in healthy elderly people (Singh et al 2002). It is also required for collagen synthesis and metabolism, and has been shown to reduce arterial stiffness and platelet aggregation in healthy male volunteers, smokers and non-smokers, and diabetics (Schindler et al 2002, Wilkinson et al 1999). These effects are often observed with doses several times higher than current RDI levels. In vivo studies further indicate that vitamin C decreases carotid wall thickness, down-regulates inducible nitric oxide synthase (iNOS) expression, normalises gene expression of antioxidant enzymes and inhibits plaque maturation (Kaliora et al 2006). Villacorta

et al (2007) assessed the combination of Vitamin C and E and concluded that the combination is able to protect the damaged vascular wall not only by limiting cell proliferation, but also by mediating the process that leads to the stabilisation of a fibrous cap by influencing components of the extracellular matrix.

Clinical studies involving vitamin C supplementation

In the pooled analysis from the Pooling Project of Cohort Studies on Diet and Coronary Disease, those subjects with higher supplemental vitamin C intake (median intake of 756 mg/day) had a 24% reduced risk of coronary heart disease than those in the lowest quintile, whereas dietary vitamin C had no significant protective effect (Knekt et al 2004). The lower risk was independent of non-dietary risk factors and related to dose. The researchers also adjusted for many relevant constituents of foods (e.g. dietary fibre and saturated fat) and found this adjustment had no effect on the association.

The recent Women's Antioxidant Cardiovascular Study (WACS) tested the effects of vitamin C (500 mg daily), vitamin E (600 IU every other day) and beta-carotene (50 mg every other day) on the combined outcome of myocardial infarction (MI), stroke, coronary revascularisation or cerebrovascular disease (CVD) death among 8171 female health professionals at increased risk. Participants were 40 years of age or older, with a prior history of CVD or three or more CVD risk factors, and were followed for an average 9.4 years. The study's factorial design enabled a comparison to be made between individual test agents as well as combination therapy. Overall, there was no significant effect for the individual nutrients vitamin C, vitamin E or beta-carotene on the primary combined endpoint, or on the individual secondary outcomes of MI, stroke, coronary revascularisation or CVD death. A marginally significant reduction in the primary outcome with active vitamin E was observed among the pre-specified subgroup of women with prior CVD (RR = 0.89, $P = 0.04$). With regard to combination therapy, people receiving both vitamins C and E experienced fewer strokes ($P = 0.03$), but there were no other significant findings (Cook et al 2007).

Effects on blood pressure

Although epidemiological evidence and prospective clinical trials point strongly to a role of vitamin C in reducing blood pressure in hypertensive and normotensive subjects, controlled studies have been inconsistent (Houston 2005). Interpretation of these results is difficult, as some studies lack a control group, have no baseline readings, use variable vitamin C doses and population characteristics, and do not report serum vitamin C or oxidative stress status. Overall, it appears that doses between 100 mg and 1000 mg of vitamin C daily are required for a reduction in blood pressure, with greater reduction in systolic blood pressure (SBP) than diastolic blood pressure (DBP) and greater response in people with higher initial value.

A 1997 review of epidemiological studies showed some inverse associations between SBP, DBP or both and vitamin C plasma concentration or intake (Ness et al 1997). Three more recent studies have supported this finding (Bates et al 1998, Block 2002, Block et al 2001). Over the past 10 years, four intervention studies investigated the effects of vitamin C supplementation, with three producing positive results (Duffy et al 1999, Fotherby et al 2000, Galley et al 1997, Ghosh et al 1994). The doses used were typically 250 mg twice daily for a period of 6–8 weeks, although effects have been reported after 4 weeks' treatment.

The negative study by Ghosh et al showed a significant reduction in both SBP and DBP with ascorbic acid. This became non-significant when compared with the placebo responses, although the placebo and ascorbic acid groups were not evenly matched for baseline plasma ascorbate concentration.

Additionally, plasma ascorbate concentrations have been shown to be inversely correlated to pulse rate in one cross-sectional study involving 500 subjects (Bates et al 1998).

Nitrate tolerance

Preliminary studies seem to support the role of vitamin C in attenuating the development of nitrate tolerance. Three human studies have found that vitamin C administration prevents the development of nitrate tolerance (Bassenge et al 1998, Watanabe et al 1998a, 1998b). Although the mechanism responsible is not yet known, results from a double-blind study using an acute dose of 2 g have suggested that vitamin C is likely to protect nitric oxide from inactivation by oxygen free radicals (Wilkinson et al 1999), which could in part explain its observed effects.

Myocardial infarction (MI)

Two prospective studies in men have suggested that ascorbic acid deficiency and marginal deficiency predict subsequent MI, independent of classical risk factors.The first, a 5-year prospective population study of 1605 middle-aged Finnish men, free of coronary disease at baseline, found that a significantly higher percentage (13.2%) of the 91 men with baseline plasma vitamin C concentrations less than 11.4 micromol/L (2.0 mg/L) experienced MI, compared with men with higher plasma vitamin C levels (Nyyssonen et al 1997). These results are particularly impressive because low plasma ascorbate was the strongest risk factor of all the measured factors. The second, a 12-year follow-up study, revealed a significantly increased relative risk of ischaemic heart disease and stroke at initially low plasma levels of vitamin C (< 22.7 micromol/L), independently of vitamin E and of the classical cardiovascular risk factors (Gey et al 1993).

In contrast, one smaller study involving 180 male patients with a first acute MI, but no recent angina, failed to detect an association between low plasma concentration of vitamin C and the risk of acute myocardial infarction (Riemersma et al 2000).

There is a large body of evidence that reactive oxygen species produced during myocardial ischaemia and reperfusion play a crucial role in myocardial damage and endothelial dysfunction. As a result, there has been some investigation to determine whether antioxidant supplementation (chiefly vitamins C and E) may improve the clinical outcome of patients with acute MI and limit the size of the infarct.

According to a large, randomised, double-blind, multicentre trial of 800 patients (mean age 62 years) with acute MI and receiving standard care, co-treatment with vitamin C (1000 mg/12 h infusion) followed by 1200 mg/day orally and vitamin E (600 mg/day) for 30 days resulted in significantly less frequent incidence of re-infarction and other post-MI complications compared to a placebo (14% versus 19% respectively) (Jaxa-Chamiec et al 2005). Another randomised, double-blind, placebo-controlled study of 37 patients with acute MI investigated the effects of starting supplementation with vitamins C and E (600 mg/day each) on the first day of symptoms and continuing for a further 14 days (Bednarz et al 2003). Active treatment resulted in significantly lower exercise-induced QT-interval dispersion (QTd) compared to a placebo, although baseline QTd was similar in both groups. A prospective, randomised study of 61 patients further suggests that oral vitamin C administration (1 g/day) could be beneficial for patients at higher thrombotic risk post-MI, such as those with diabetes (Morel et al 2003).

Cancer: prevention and treatment

One of the most important modifiable determinants of cancer risk is diet. Several research panels and committees have independently concluded that high fruit and vegetable intake decreases the risk of many types of cancer and, because vitamin C is present in large quantities in these foods, it is plausible that the reduction in cancer risk associated with the consumption of fruits and vegetables may be, at least in part, attributable to dietary vitamin C (Li & Schellhorn 2007).

Prevention

Epidemiological evidence of a protective effect of dietary vitamin C for non-hormone-dependent cancers is strong (Block 1991a, 1991b). The majority of studies in which a dietary vitamin C intake was calculated have identified a statistically significant protective effect, with high intake conferring approximately a twofold protective effect compared with low intake. In general, most have shown that higher intakes of vitamin C are associated with decreased incidence of cancers of the mouth, throat and vocal chords, oesophagus and stomach, pancreas, colon, rectum, renal cell and lung (Cohen & Bhagavan 1995, FAO/WHO 2002, Jenab et al 2006, Negri et al 2000, You et al 2000). More recently, a case control study of men in New York found that a higher intake of vitamin C was associated with reduced risk of prostate cancer (McCann et al 2005).

Clinical note — Vitamin C for cancer: a historical perspective

More than three decades ago, the well-known team of Ewan Cameron and Linus Pauling started investigating the effects of high doses of continuous intravenous vitamin C and oral supplements in treating advanced, incurable cancer. The idea of using vitamin C was born out of the recognition that the outcome of every cancer is determined to a significant extent by the individual's inherent resistance, which in turn is influenced by the availability of certain nutritional factors such as ascorbic acid (Cameron 1982). They have published the results of several trials that have shown enhanced quality of life for some terminal patients and also improvements in objective markers. As a result, a protocol for the use of vitamin C in the treatment of cancer has been developed at the Vale of Leven Hospital, the chief site of Cameron and Pauling's investigations (Cameron 1991). The protocol emphasises the importance of using an initial course of intravenous ascorbate, followed by a maintenance oral dose. Although their results are encouraging, they have been criticised because randomised double-blind principles were not adopted.

Two other large studies have identified inverse associations between dietary vitamin C and breast cancer risk (Michels et al 2001, Zhang et al 1999). More specifically, the Nurses' Health Study, which involved 83,234 women, detected a strong inverse association between total vitamin C from foods and breast cancer risk among premenopausal women with a positive family history of breast cancer (Zhang et al 1999). Those who consumed an average of 205 mg/day of vitamin C from foods had a 63% lower risk of breast cancer than those who consumed an average of 70 mg/day. A large Swedish population-based prospective study that comprised 59,036 women found that high dietary intakes of ascorbic acid (mean intake 110 mg/day) reduced the risk of breast cancer among women who were overweight and/or had a high intake of linoleic acid (Michels et al 2001).

More recently, a case–control study nested within the European Prospective Investigation into Cancer and Nutrition (EPIC) identified an inverse risk of gastric cancer in the highest versus lowest quartile of plasma vitamin C (Jenab et al 2006). The inverse association was more pronounced in subjects consuming higher levels of red and processed meats, a factor that may increase endogenous N-nitroso compound production. It has been proposed that vitamin C protects against gastric cancer because it inhibits carcinogenic N-nitroso compound production in the stomach and acts as a free-radical scavenger.

Overall, it appears that the protective effect is dose-dependent, with studies finding significant cancer risk reductions in people consuming at least 80–110 mg of vitamin C daily in the long term (Carr & Frei 1999).

Clinical studies

One of the first published studies by Cameron and Pauling (1974) was a Phase I–II study in 50 patients with advanced, untreatable malignancies, in which both subjective and objective markers were evaluated. They observed that 27 patients failed to respond to treatment; however, three patients experienced stabilisation of disease, tumour regression occurred in five patients and tumour haemorrhage and necrosis occurred in four patients. Two years later, the same research team published a report that compared the survival rates of 100 terminal cancer patients given supplemental ascorbate as part of their routine management with 1000 patients who were not given the supplement, and observed the mean survival time to be more than 4.2 times longer for the ascorbate subjects (> 210 days) than for the controls (50 days) (Cameron & Pauling 1976).

In subsequent years, two randomised, placebo-controlled studies investigating the effects of oral vitamin C supplementation (10 g/day) in terminal cancer patients failed to detect a significant difference in outcome (Creagan et al 1979, Moertel et al 1985). These two studies are often cited as evidence disproving the benefits of vitamin C in cancer treatment; however, the different routes of administration investigated in these studies is an important factor central to the discrepant results (Padayatty & Levine 2000). Maximal plasma vitamin C concentrations achievable by oral administration are limited by the kidney, which eliminates excess ascorbic acid through renal excretion, whereas IV injection bypasses the renal absorptive system, resulting in elevated plasma concentrations to high levels. As such, it has been argued that only IV administration of high-dose ascorbate can produce millimolar plasma concentrations that are toxic to many cancer cell lines.

Scientific interest in the interaction between ascorbic acid and cancer has been reawakened in recent years, with new evidence that in millimolar concentrations (only achievable after parenteral administration) vitamin C is selectively cytotoxic to many neoplastic cell lines, potentiates cytoxic agents and demonstrates anticancer activity alone and in combination with other agents in tumour-bearing rodents (Hoffer et al 2008). Simultaneously, theoretical interest has arisen in the potential of redox-active molecules like menadione, trolox and ascorbic acid to modify cancer biology, especially when administered with cytotoxic drugs.

Intravenous vitamin C

Intravenous administration of vitamin C achieves much higher plasma and urine concentrations than oral dosing and has been proposed as the only viable means of achieving the high concentrations required to induce the antitumour effects exhibited by the vitamin (Padayatty et al 2004). Case studies suggest that this approach can improve patient well-being and, in some cases, reduce tumour size and improve survival (Padayatty et al 2006, Riordan et al 2005).

A safety study conducted in 2005 involved 24 late-stage terminal cancer patients who were administered continuous vitamin C infusions of 150–710 mg/kg/day for up to 8 weeks (Riordan et al 2005). This treatment regimen increased plasma ascorbate concentrations to a mean of 1.1 mmol/L and was considered relatively safe. The most common side effects reported were nausea, oedema and dry mouth or skin, and two 'possible' adverse events occurred. One was a patient with a history of renal calculi who developed a kidney stone after 13 days of treatment, and another was a patient who experienced hypokalaemia after 6 weeks. Interestingly, the majority of patients were vitamin-C-deficient before treatment.

Clinical trials for phases I and II are currently being conducted using intravenously administered vitamin C in patients with solid tumours. The phase I study was primarily conducted to determine a recommended phase 2 dose, with secondary objectives to define any toxic effects, detect any preliminary antitumour effects and monitor for preservation of or improvement in quality of life. In the first phase I trial published in 2008, patients with advanced cancer or haematologic malignancy were assigned to sequential cohorts infused with 0.4, 0.6, 0.9 and 1.5 g ascorbic acid/kg body weight three times weekly, delivered intravenously. This protocol achieved plasma ascorbic acid concentrations of > 10 μM for more than 4 hours, which is considered sufficient to induce cancer cell death according to in vitro research. In addition, all patients were provided with a daily multivitamin tablet (Centrum Select, Wyeth) and 400 IU d-alpha-tocopherol twice daily with meals, and, on non-infusion days, 500 mg ascorbic acid twice daily to obviate large shifts in plasma ascorbic acid concentrations. No unusual biochemical or haematologic abnormalities were observed, and there were no changes in the social, emotional or functional parameters of quality of life in any cohort. Unlike in the previous case series by Cameron and Pauling (1974), in which acute tumour haemorrhage and necrosis were reported, these effects were not seen in this study (Hoffer et al 2008). Researchers concluded that the promise of ascorbic acid in the treatment of advanced cancer may lie in its combination with cytotoxic agents, where high concentrations might modify either toxicity or response. A phase I–II clinical trial is being planned that will combine IV ascorbic acid with chemotherapy as a first-line treatment in advanced stage non-small-cell lung cancer, using the dose determined from this study.

Based on the available evidence of antitumour mechanisms and these case reports, further research into this approach is clearly warranted.

Adjunct to oncology treatments

Whether vitamin C improves or hinders responses to standard oncology treatment has been the focus of intense debate for many decades. There are in vitro studies showing that vitamin C can enhance the antitumour activity of cisplatin and doxorubicin (Abdel-Latif et al 2005, Kurbacher et al 1996, Reddy et al 2001, Sarna & Bhola 1993). In vivo evidence shows vitamin C enhances the effectiveness of 5-fluorouracil, doxorubicin, cyclophosphamide and vincristine (Lamson & Brignall 2000, Nagy et al

Clinical note — The debate continues … to vitamin C or not?

One research group based at the University of Colorado has produced evidence that suggests that vitamin C and other antioxidant nutrients may not only protect healthy cells from damage, but also improve the antitumour effects of standard treatment (Gottlieb 1999). They are currently conducting further research to identify how cell selectivity occurs, but propose that cancer cells may have lost the normal homeostatic regulatory mechanism that stops excessive concentrations of antioxidants from entering the cell. As intracellular levels rise, a series of reactions occurs, resulting in growth inhibition and cell death. Another group at Memorial Sloan Kettering Cancer Centre (Gottlieb 1999) argues that tumours already contain higher levels of ascorbic acid than normal cells and have identified a mechanism to explain this observation. As such, they advocate against the use of vitamin C when cytotoxic agents that rely on free-radical production are being used (see Ch 10 for further discussion).

2003), whereas other studies find no change in drug effect. Although these results are promising, no large randomised studies are available to confirm their significance in humans.

Most recently, vitamin C inactivated the effects of bortezomib, a new proteasome inhibitor approved by the US Food and Drug Administration for the treatment of patients with relapsed multiple myeloma (Zou et al 2006). Interestingly, drug inactivation was not achieved through antioxidative mechanisms.

Evidence from experimental models suggests that vitamin C may also reduce drug toxicity in a dose-dependent manner (Giri et al 1998, Greggi Antunes et al 2000).

Diabetes

Vitamin C has several actions that provide a basis for its use in diabetes. It has been reported to lower erythrocyte sorbitol concentrations (important for preventing complications in type 1 diabetes), improve endothelial function (important for slowing atherosclerosis) and reduce blood pressure (Beckman et al 2001, Cunningham 1998). Plasma vitamin C levels seem to play a role in the modulation of insulin activity in aged healthy or diabetic subjects (Paolisso et al 1994) and are inversely related to glycosylated haemoglobin. Additionally, increased free-radical production has been reported in patients with diabetes mellitus as a result of hyperglycaemia, which directly induces oxidative stress (Ceriello et al 1998).

Blood glucose

At this stage there are few studies that test the effects of supplemental vitamin C on plasma glucose levels directly. Although one early study demonstrated that an oral dose of 1500 mg vitamin C reduces plasma glucose levels in patients with type 2 diabetes (Sandhya & Das 1981), no further published studies confirm this result.

Endothelial function

The results of studies investigating the role of vitamin C on endothelial function in diabetes have attracted recent interest.

A double-blind, placebo-controlled study demonstrated that chronic oral vitamin C supplementation (500 mg/day) in type 2 diabetes significantly lowered arterial blood pressure and improved arterial stiffness compared with a placebo (Mullan et al 2002). After 1 month's treatment, SBP fell from 142.1 to 132.3 mmHg, mean pressure from 104.7 to 97.8 mmHg, DBP from 83.9 to 79.5 mmHg and peripheral pulse pressure from 58.2 to 52.7 mmHg, whereas placebo had no effect.

A randomised study of women with a history of gestational diabetes showed that ascorbic acid supplementation resulted in a significant improvement of endothelium-dependent flow-mediated dilatation, with no effect seen for a placebo (Lekakis et al 2000).

However, a randomised, double-blind, placebo-controlled study of vitamin C (800 mg/day for 4 weeks) concluded that high-dose oral vitamin C therapy resulted in incomplete replenishment of vitamin C levels and does not improve endothelial dysfunction and insulin resistance in type 2 diabetes (Chen et al 2006).

The mechanism of action appears to involve several steps, such as reduction in LDL oxidation, enhanced endothelial NO synthase activity and NO bioavailability and reduced insulin resistance, which can cause endothelium-dependent, NO-mediated vasodilation.

Eye health

Diabetes mellitus is associated with a number of ocular complications that can eventually lead to blindness. Vitamin C is found in high concentration in the eye and is thought to be important for protection against free radicals. This may have special significance for people with diabetes mellitus, as most studies have found that their circulating vitamin C levels are at least 30% lower than in people without the disease (Peponis et al 2002). One study demonstrated that a combination of oral vitamins C (1000 mg/day) and E (400 IU/day) improved tear film stability, tear secretion and the health of the ocular surface in diabetic patients.

Because of its safety, cost effectiveness and generally encouraging results, a strategy of adding 200–600 mg of vitamin C to a healthy diet is worth considering for individuals with diabetes type 1 or 2.

Prevention of cataracts

Ascorbate has long been known to accumulate in tears and other biofluids, such as cerebrospinal fluid relative to plasma (Patterson & O'Rourke 1987), and lowered levels of vitamin C in the eye have been associated with increased oxidative stress in the human cornea (Shoham et al 2008). Ascorbic acid is thought to be a primary substrate in ocular protection because of its high concentration in

the eye. Within the cell, vitamin C helps to protect membrane lipids from peroxidation by recycling vitamin E (May 1999). It is present at high concentrations in vitreous humor (Hanashima & Namiki 1999), cornea (Brubaker et al 2000) and tear film (Dreyer & Rose 1993).

Numerous observational and prospective clinical studies have been performed to examine the effect on cataracts of vitamin C alone or in combination with other antioxidants. Several epidemiological studies have identified an association between vitamin C and cataract incidence (Ferrigno et al 2005, Jacques & Chylack Jr 1991, Jacques et al 1988, Valero et al 2002); however, studies investigating whether supplementation is protective have produced mixed results (Chasan-Taber et al 1999, Chylack Jr et al 2002, Hammond & Johnson 2002, Jacques et al 1997, 2001, Kuzniarz et al 2001, Seddon et al 1994, Taylor et al 2002).

Results from the Harvard Nurses' Health Study, Physicians' Health Study, the Beaver Dam Eye Study and the Australian Blue Mountains study suggest that if protective effects are to be seen, they are most likely when vitamin C is taken for a long period (5–10 years or more) and/or used as part of a multivitamin combination (Kuzniarz et al 2001, Mares-Perlman et al 2000, Seddon et al 1994, Taylor et al 2002).

It is suspected that vitamin C protects the lens of the eye from oxygen-related damage over time by both direct free-radical scavenging activity and indirect activity. This is achieved primarily by protecting endogenous alpha-tocopherol (the major lipid-soluble antioxidant of retinal membranes) against oxidation induced by UV radiation and by regenerating it (Stoyanovsky et al 1995).

Atopy and asthma

Vitamin C is the major antioxidant present in the extracellular fluid lining of the lung, where it protects against both endogenous free radicals (produced as a by-product of inflammation) and environmental free radicals (such as ozone in air pollution). According to many epidemiological studies, dietary intake of vitamin-C-rich foods or serum ascorbate is associated with improved lung function in both asthmatic and normal subjects (Devereux & Seaton 2005, McDermoth 2000, Kelly 2005). Oxygen metabolites can play a direct or indirect role in the modulation of airway inflammation. Many studies suggest that superoxide dismutase and free-radical scavengers in the blood are significantly lower in asthma, and document a correlation between asthmatic severity and ROS products in asthmatic subjects (Shanmugasundaram 2001, Vural 2000). Not surprisingly, low blood concentrations of vitamin C have been found in mild asthmatic subjects (Rahman 2006).

Despite a theoretical basis for its use in lung diseases such as asthma, its value in this disease is controversial. A 2001 Cochrane Review of three studies concluded that current evidence is insufficient to recommend a specific role for vitamin C in the treatment of asthma and that a large-scale RCT is required to clarify its role (Kaur et al 2001).

Clinical note — Do asthmatic lungs need more antioxidant protection?

In 1999, Kelly et al found that people with mild asthma have low levels of antioxidant nutrient vitamins E and C in their lung lining fluid, even though blood levels of these vitamins may be normal or increased. This observation, together with other factors, indicated that the asthmatic lung is exposed to greater oxidative stress in people with asthma than in non-asthmatics. The researchers suggested that the inflammatory cells in the lungs of asthmatic patients generate more free-radical species than those in healthy people, adding to bronchoconstriction, increased mucus secretion and increased airways responsiveness. Given that oral supplementation in asthma has produced inconsistent results, chief researcher Frank Kelly suggests that future studies should focus on other administration forms such as vitamin C inhalers (personal communication, Melbourne, 1998).

An updated Cochrane Review published in 2004 included new data from a study of 201 adults taking inhaled corticosteroids and came to a similar conclusion, stating that evidence is currently conflicting (Ram et al 2004).

Alternatively, the evidence for its use in exercise-induced asthma appears stronger, as three human studies have produced positive results when vitamin C was used as pretreatment in doses ranging from 500 mg to 2000 mg (Cohen et al 1997, Miric & Haxhiu 1991, Schachter & Schlesinger 1982).

Bone mineral density

Although the relationship between calcium, vitamin D and bone mineral density (BMD) is well known, other nutrients, such as vitamin C, are also critical for bone development, repair and maintenance (Ilich et al 2003).

Data collected from 13,080 adults enrolled in the Third National Health and Nutrition Examination Survey (NHANES III) from 1988 to 1994 have identified an association between dietary and serum ascorbic acid, BMD and bone fracture (Simon & Hudes 2001). Dietary ascorbic acid intake was independently associated with BMD among premenopausal women and postmenopausal women without a history of smoking or oestrogen use. Additionally, fracture risk fell by 49% in postmenopausal women (with a history of smoking and oestrogen use) who had high serum vitamin C levels.

Vitamin C supplementation

Two controlled studies have investigated the effects of long-term vitamin C supplementation in postmenopausal women and found that it increases BMD (Hall & Greendale 1998, Morton et al 2001). Both studies identified a positive association with BMD in postmenopausal women with dietary calcium intakes of at least 500 mg or those taking calcium supplements. The effect was especially marked in those women taking calcium supplements and concurrent HRT.

The daily dose taken was generally in excess of the RDI and ranged from 100–5000 mg. More specifically, one study found that for each 100 mg increment in dietary vitamin C intake there was an associated increase of 0.017 g/cm^2 in BMD (femoral neck and total hip), and for those women with calcium intakes above 500 mg/day the increment increased to 0.019 g/cm^2 in BMD per 100 mg vitamin C.

A recent Australian study of 533 randomly selected women determined that vitamin C supplements may suppress bone resorption in nonsmoking postmenopausal women (Pasco et al 2006).

In contrast to these results, no effect on BMD was observed for dietary or supplemental vitamin C in the Women's Health Initiative Observational Study and Clinical Trial, which involved 11,068 women aged 50–79 years (Wolf et al 2005). However, a significant beneficial interaction was observed between total vitamin C and HRT on total-body, femoral neck, spine and total-hip BMD.

Animal studies have detected an improved healing response in bone fractures with supplemental vitamin C, suggesting a further role in fracture healing (Yilmaz et al 2001).

Sports

Vitamin C supplementation is often used by athletes in order to improve recovery, restore immune responses, enhance wound healing, and counteract oxidative stress and changes to adrenal hormones and inflammatory responses. It is often taken together with other antioxidant vitamins and minerals, such as vitamin E and zinc. One placebo-controlled study has shown that 20 mg of ascorbic acid twice daily over 14 days has some modest beneficial effects on recovery from unaccustomed exercise (Thompson et al 2001); however, no studies have reported improved performance for vitamin C supplementation.

Prevention of post-endurance-exercise infections

Athletes often use vitamin C supplements to prevent infections, as strenuous training and physiological stress appear to increase the body's need for vitamin C to a level above the usual RDI (Schwenk & Costley 2002). Additionally, the risk of infection after an intense aerobic training session or competition (such as a marathon) is increased (Jeurissen et al 2003).

A 2004 Cochrane Review that analysed results from six trials involving a total of 642 marathon runners, skiers and soldiers on subarctic exercises found regular vitamin C supplementation significantly reduced the incidence of the common cold, supporting its use in this population (Douglas et al 2004).

Alterations to neurotransmitters and adrenal hormone

Several studies have been conducted with ultramarathon runners to investigate whether vitamin C supplementation, usually in doses of 1500 mg/day, is able to restore exercise-induced changes to neurotransmitters, adrenal hormones or inflammatory responses (Nieman et al 2000, Peters et al 2001a, Peters et al 2001b). Overall, it appears that high-dose vitamin C supplements taken at least 7 days before racing does have some effect.

One study involving 45 ultra-marathon runners found that doses of 1500 mg vitamin C taken for 7 days before the race, on the day of the race and for 2 days following the race significantly attenuated exercise-induced elevations in cortisol, adrenaline and IL-10 and IL-1 receptor antagonist levels compared with a placebo (Peters et al 2001a); however, the effect was transient.

Male infertility

A relationship between infertility and the generation of ROS has been established and extensively studied. Alterations in the testicular microenvironment and haemodynamics can increase production of ROS and/or decrease local antioxidant capacity, resulting in generation of excessive oxygen species (OS). A large number of studies have elucidated the effects of increased OS in the serum, semen and testicular tissues of patients.

Vitamin C (ascorbic acid), a major antioxidant found in extracellular fluid, is present in seminal fluid at a high concentration compared with that in blood plasma (364 versus 40 μM) and is present in detectable amounts in sperm (Patel & Sigman 2008). In infertile men, vitamin C has been found in reduced quantity in the seminal plasma (Lewis et al 1997). An association between oxidative stress and sperm DNA fragmentation has been identified and has led to studies looking for changes in semen DNA fragmentation as an outcome rather than just changes in semen parameters.

A review of the literature reveals that interventional studies have produced promising but inconsistent results and incomplete reporting of study outcomes. Sometimes changes to semen parameters are noted, but there is little or no information about successful pregnancies or characteristics of the study population, thereby hindering accurate interpretation of results. Clearly further research is required to better evaluate the effects of vitamin C in male fertility.

An RCT of 75 fertile, heavy smokers compared placebo to two different doses of vitamin C (200 mg and 1000 mg) and found that both supplemented groups experienced a significant improvement in sperm concentration, morphology and viability (Dawson et al 1992).

A randomised, placebo-controlled trial found that treatment with oral vitamin C and E of men with unexplained infertility associated with elevated sperm DNA fragmentation led to decreased DNA fragmentation without a change in semen parameters (Greco et al 2005b).

In an uncontrolled study of 38 men with an elevated percentage of fragmented spermatozoa (R 15%) and one prior failed intracytoplasmic sperm injection (ICSI) attempt, oral supplementation with vitamins E and C demonstrated a significant improvement in pregnancy rate (48.2% versus 6.9%) and implantation rate (19.6% versus 2.2%) when compared with their prior ICSI attempt (Greco et al 2005a).

Adjunct therapy for haemodialysis patients

Recent research highlights that vitamin C can potentiate the mobilisation of iron from inert tissue stores, and facilitates the incorporation of iron into protoporphyrin in haemodialysis patients being treated with epoetin. Eighteen published studies in the past decade have addressed this issue (Attallah et al 2006, Chan et al 2005, Deira et al 2003, Gastaldello et al 1995, Giancaspro et al 2000, Hörl 1999, Keven et al 2003, Lin CL et al 2003, Macdougall 1999, Mydlik et al 2003, Nguyen 2004, Sezer et al 2002, Taji et al 2004, Tarng & Huang 1998, Tarng et al 1999a, Tarng et al 1999b,Tarng et al 2004, Tovbin et al 2000).

Administration of intravenous vitamin C to haemodialysis patients with functional iron deficiency may promote better anaemia control and iron utilisation and has also been used successfully in patients with iron overload (Tarng & Huang 1998, Tarng et al 1999a, Tarng et al 1999b).

OTHER USES

Vitamin C is used for numerous indications, although many have not been significantly studied, such as irritable bowel syndrome, osteoarthritis, menopausal hot flushes, cervical dysplasia, prevention of Alzheimer's dementia, allergies, treatment of lead toxicity and reducing delayed-onset muscle soreness.

Vitamin C supplements have also been used as part of antioxidant combination therapy in HIV and in heroin withdrawal. Preliminary research has shown that some antioxidant combinations reduce oxidative stress (Jaruga et al 2002), induce immunological and virological effects that might be of therapeutic value (Muller et al 2000) and produce a trend towards a reduction in viral load in HIV (Allard et al 1998). High doses of oral ascorbic acid and vitamin E may ameliorate the withdrawal syndrome of heroin addicts after 4 weeks' treatment, according to one study (Evangelou et al 2000).

DOSAGE RANGE

Australian and New Zealand RDI

- Children
  - < 8 years: 35 mg.
  - 9–19 years: 40 mg.
- Adults
  - >19 years: 45 mg.
- Pregnancy
  - < 19 years: 55 mg.
  - > 19 years: 60 mg.
- Lactation
  - <19 years: 80 mg.
  - >19 years: 85 mg.

Deficiency

- 100 mg taken 3–5 times daily until 4000 mg has been administered, followed by a maintenance dose of 100 mg/day and encouragement to eat a diet with fresh fruit and vegetables.
- In cases of acute infection, CAM practitioners frequently recommend vitamin C in doses of 1000 g (or more), to be taken in divided doses every few hours until loose bowels are experienced, otherwise known as 'bowel tolerance'. The rationale behind this dosage regimen is that body requirements during infection are dramatically increased, and not only does high-dose vitamin C meet these needs, but also maximum vitamin C absorption is attained when it is taken in divided doses rather than one large amount.

According to clinical studies

- Asthma: 500–2000 mg before exercise.
- Cancer: 10–100 g/day IV.
- Cardiovascular disease prevention: up to 1000 mg/day long term.
- Bone mineral density: 750 mg/day long term.
- Cataract protection: 500 mg/day long term.
- Diabetes: 0.5–3 g/day long term.
- Histamine-lowering effects: 250 mg to 2 g/day for several weeks.
- Respiratory infection: 1–2 g/day.
- Sunburn protection: oral vitamin C (2000 mg/day) in combination with vitamin E (1000 IU/day).
- Urinary acidification: 4–12 g taken in divided doses every 4 hours.

ADVERSE REACTIONS

Adverse effects of oral vitamin C include loose bowels and diarrhoea with high-dose supplements; however, the dose at which this occurs varies between individuals and also varies for each individual at different times.

SIGNIFICANT INTERACTIONS

Aluminium-based antacids

Vitamin C increases the amount of aluminium absorbed. Separate doses by at least 2 hours.

Aspirin

Aspirin may interfere with both absorption and cellular uptake mechanisms for vitamin C, thereby increasing vitamin C requirements (observed in animal and human studies). Increased vitamin C intake may be required with long-term therapy (Basu 1982).

Chitosan

According to a preliminary study in rats, taking vitamin C in combination with chitosan might provide additional benefit in lowering cholesterol. Potentially beneficial interaction.

Cisplatin

Vitamin C enhanced the antitumour activity of cisplatin in several in vitro tests (Abdel-Latif et al 2005, Sarna & Bhola 1993, Reddy et al 2001) and reduced drug toxicity in experimental models (Giri et al 1998, Greggi Antunes et al 2000). Potentially beneficial but difficult to assess.

Corticosteroids

Corticosteroids may increase the requirement for vitamin C based on in vitro and in vivo data (Chowdhury & Kapil 1984, Levine & Pollard 1983). Increased intake may be required with long-term drug therapy.

Cyanocobalamin
Vitamin C can reduce absorption of cyanocobalamin. Separate doses by at least 2 hours.

Cyclophosphamide
Vitamin C enhanced the therapeutic drug effect in vivo (Lamson & Brignall 2000). Potentially beneficial but difficult to assess.

Doxorubicin
Vitamin C enhanced the therapeutic drug effect and reduced drug toxicity in vivo (Lamson & Brignall 2000). Potentially beneficial but difficult to assess.

Etoposide
Vitamin C enhanced the antitumor activity of etoposide in vitro (Reddy et al 2001). Potentially beneficial but difficult to assess.

Fluorouracil
Vitamin C enhanced the antitumour activity of 5-fluorouracil in vitro and in vivo (Abdel-Latif et al 2005, Nagy et al 2003). Potentially beneficial but difficult to assess.

Iron
Vitamin C increases the absorption of iron. Potentially beneficial interaction.

L-Dopa
A case report of co-administration with vitamin C suggests this may reduce drug side effects (Sacks & Simpson 1975). Beneficial interaction.

Tamoxifen
Vitamin C enhanced the antitumour activity in vitro (Lamson & Brignall 2000). Potentially beneficial but difficult to assess.

Vincristine
Vitamin C enhanced the drug's effect in vivo (Lamson & Brignall 2000). Potentially beneficial but difficult to assess.

PS-341 (Bortezomib, Velcade)
This is a proteasome inhibitor approved by the USFDA for the treatment of patients with relapsed multiple myeloma. Vitamin C inactivated drug activity in vitro (Zou et al 2006). Avoid until safety can be established.

CONTRAINDICATIONS AND PRECAUTIONS
In patients who are sensitive to iron overload, vitamin C supplementation may exacerbate iron toxicity by mobilising iron reserves. As such, vitamin C supplementation should be used with caution by people with erythrocyte glucose-6-phosphate dehydrogenase deficiency, haemochromatosis, thalassaemia major or sideroblastic anaemia.

Intravenous vitamin C
A dose-response study involving patients with solid tumours receiving high-dose IV vitamin C found virtually all the side effects that occurred were consistent with the side effects attending the rapid infusion of any high-osmolarity solution. The symptoms were preventable by encouraging patients to drink fluids before and during the infusion. Indeed, rather than provoking fluid overload, ascorbic acid acted like an osmotic diuretic which could induce volume depletion if patients did not compensate by increasing their voluntary fluid intake. Therefore, contraindications to the infusion of very-high-osmolarity ascorbic acid infusions are the same as for other osmotic diuretics: anuria, dehydration, severe pulmonary congestion or pulmonary oedema and a fixed low cardiac output (Hoffer et al 2008).

Clinical note — Does vitamin C interact with the OCP?
In 1981 a case was reported of a woman who had experienced heavy breakthrough bleeding as a result of stopping vitamin C supplementation while taking the oral contraceptive pill (Morris et al 1981). At the time, it was suspected that vitamin C in high doses increases the bioavailability of oestrogen and raises blood concentrations due to competition for sulfation (resulting in reduced drug metabolism) (Back & Orme 1990). Therefore, ceasing supplement use would have the opposite effect and potentially cause breakthrough bleeding, as reported in this case. Since then, further investigation has been conducted to investigate whether this interaction is clinically significant. In 1993 a placebo-controlled study was conducted with 37 women and found that 1000 mg of vitamin C does not lead to an increased systemic bioavailability of ethinyl oestradiol, and therefore the purported interaction is unlikely to be of any clinical importance (Zamah et al 1993).

Laboratory tests
Supplemental vitamin C can affect the results of numerous laboratory tests and should be stopped prior to:
- carbamazepine
- lactate dehydrogenase
- serum AST
- serum bicarbonate
- serum cholesterol
- serum creatinine
- serum creatine kinase
- serum HbA_{1c}
- serum phosphate
- serum triglycerides
- serum urea nitrogen
- stool guiac
- theophylline
- urine 17-hydroxy corticosteroids
- urine 17-ketosteroids
- urine amphetamine
- urine and serum bilirubin
- urine and serum glucose
- urine and serum uric acid
- urine barbiturate
- urine beta-hydroxybutyrate

- urine iodide
- urine oxalate
- urine paracetamol
- urine protein.

PREGNANCY USE

Vitamin C is safe in pregnancy.

PATIENTS' FAQs

What will this vitamin do for me?

Vitamin C is necessary for health and wellbeing. Supplements have also been used for a variety of indications and in some cases shown to have benefits.

When will it start to work?

Studies have found that dietary or supplemental vitamin C may be required for at least 10 years before protection against heart disease or cancer incidence is detected. However, other benefits may be experienced more quickly, depending on the dose used and indication.

Are there any safety issues?

Vitamin C is considered very safe, although high doses may induce reversible loose bowels or diarrhoea. Supplements should be taken only under medical supervision by people with erythrocyte glucose-6-phosphate dehydrogenase deficiency, haemochromatosis, thalassaemia or sideroblastic anaemia.

Clinical note — Is the kidney stone risk overstated?

Most kidney stones consist of calcium oxalate, and higher urinary oxalate increases the risk of calcium oxalate nephrolithiasis (Taylor & Curhan 2007). Four mechanisms have been identified that account for increased oxalate excretion: increased dietary intake of oxalate, abnormally increased intestinal absorption of oxalic acid, a deficiency of oxalate-degrading bacteria (in particular *Oxalobacter formigenes*) and increased endogenous production of oxalate. Vitamins C and B_6 are both involved in the metabolic pathway of oxalate. While 40% of dietary vitamin C undergoes a non-enzymatic conversion to oxalate, vitamin B_6 has the opposite effect and metabolises oxalate (Gill & Rose 1985). Since vitamin C has been shown in some (but not all) studies to increase urinary oxalate, researchers speculated that it might have a detrimental role in increasing the risk of kidney stone formation.

Reports of a possible link between ascorbic acid and kidney stones started to appear in the literature in the 1980s (Griffith et al 1986, Power et al 1984). These findings have been challenged by several studies carried out in humans and in experimental animals since that time. In 1994, researchers discovered that vitamin C (in doses as high as 10 g/day) does not increase the amount of oxalate produced in the body in non-stone forming people (Wandzilak et al 1994). Instead, urine tests used to detect oxalate levels were actually detecting oxalate formed by the conversion of ascorbate during the test procedure. As such, urine oxalate levels tested by this method do not genuinely represent in vivo oxalate when ascorbate is involved. Three studies that followed found no association between vitamin C intake and kidney stone risk. Two prospective studies of more than 85,000 women and 45,000 men found that doses ranging from less than 250 mg/day to more than 1500 mg/day taken over 6–14 years did not correlate with occurrence of kidney stones (Curhan et al 1996, 1999). The third was a controlled study measuring oxalate excretion and several other biochemical and physicochemical risk factors associated with calcium oxalate urolithiasis (Auer et al 1998, Curhan et al 1996, Curhan et al 1999).

Based on the available evidence, it appears unlikely that vitamin C supplements increase the risk of nephrolithiasis in the general population, particularly if they are used in the short to medium term.

PRACTICE POINTS/PATIENT COUNSELLING

- Vitamin C is an essential nutrient for humans, as we are one of the few animal species that cannot synthesise it endogenously.
- Although vitamin C is found widely in fruit and vegetables, up to 100% can be destroyed during cooking and storing, as it is sensitive to light, heat, oxygen and alkali.
- Although frank deficiency is uncommon in Western countries, marginal deficiency states are not uncommon, particularly in young children fed exclusively on cow's milk for a prolonged period, the institutionalised or isolated elderly, chronic alcoholics, the urban poor and cigarette smokers.
- Vitamin C is an antioxidant and is involved in a myriad of biochemical processes in the body, such as neurotransmitter and hormone synthesis, maintenance of connective tissue, immune function and adrenal function.
- Many studies have found a protective effect for dietary vitamin C intake on cardiovascular disease and cancer incidence, emphasising the importance of adequate dietary intake of fresh fruit and vegetables. Positive effects have also been detected for bone density and cataract incidence.
- Oral vitamin C supplements have been investigated in many different conditions. Positive results have been obtained in some of these studies, such as for reducing duration of the common cold, coronary heart disease prevention, prevention of several cardiovascular diseases and bone mineral density. Results in cancer treatment remain controversial for oral supplements.
- New research shows that long-term supplements do not increase the risk of kidney stones and do not interact with oral contraceptives.

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Vitamin D

HISTORICAL NOTE Vitamin D was identified as a nutrient in the early 1900s, when it was first realised that cod liver oil had an antirachitic effect in infants.

BACKGROUND AND RELEVANT PHARMACOKINETICS

The name 'vitamin D' actually refers to several related fat-soluble vitamin variants, all of which are sterol (cholesterol-like) substances. Cholecalciferol (D_3) is the form found in animal products and fish oils, whereas ergocalciferol (D_2) is the major synthetic form of provitamin D typically found in supplements and fortified foods; however, other forms also exist. These ingested forms have 50–80% bioavailability and enter the lymphatic circulation from the small intestine following emulsification by bile salts. In the liver and kidneys, both D_2 and D_3 are converted to D's major circulating forms: 25-hydroxycholecalciferol (inactive) — 25(OH)D and 1,25-dihydroxycholecalciferol (active) — $1,25(OH)_2D$.

Vitamin D (D_3) is also produced in the body through the conversion of a cholesterol-based precursor, 7-dehydrocholesterol, which is produced in the sebaceous glands of the skin. Exposure to sunlight (UVB) converts this precursor into cholecalciferol over a 2–3 day period. Prolonged exposure to UVB can inactivate some of the newly formed vitamin D and its precursors, so that eventually a state of equilibrium is reached between vitamin D synthesis and catabolism. Therefore, short periods of sun exposure are considered more efficacious than long periods (Working Group 2005). Some vitamin D is stored in adipose tissue and can be mobilised during periods when exposure to sunlight is reduced or shortages develop (Nowson & Margerison 2002). Vitamin D and its metabolites are primarily excreted through bile, and the degraded active form is removed via the kidney. Losses are believed to be minor, owing to both reabsorption of vitamin D derivatives via the enterohepatic recirculation and limited filtration at the kidneys (Kohlmeier 2003). Parathyroid hormone (PTH), calcium, phosphorus and magnesium are involved in the regulation of vitamin D metabolism.

Traditionally associated with bone health, the identification of vitamin D receptors (VDR) on a large and diverse number of cells has precipitated significant reconsideration of this nutrient (Dusso et al 2005, Holick 2004, Holick 2006). Consequently, we now understand that vitamin D possesses two distinct action pathways dependent upon the site of bioactivation (Dusso et al 2005, Holick 2006). Renal hydroxylation of 25(OH)D produces $1,25(OH)_2D$, primarily responsible for its traditional endocrine actions.

Extrarenal bioactivation, by immune, prostate, breast, colon, beta and skin cells, however, results in non-genomic responses, characterised as autocrine rather than endocrine effects (Dusso et al 2005, Kemmis et al 2006, Holick 2006). Production of $1,25(OH)_2D$ at these sites does not fall under the same tight regulatory control as renal 1-alpha-hydroxylase (Dusso et al 2005, Kemmis et al 2006). This means that increasing concentrations of 25(OH)D provide a substrate for extrarenal bioactivation, with the rate of conversion mainly reliant upon local factors such as cytokines (Holick 2005b, Lips 2006).

Is vitamin D really a vitamin?

Many characteristics of the vitamin D molecules vary substantially from the orthodox definition of a vitamin (Dusso et al 2005, NHMRC 2006, Vieth 2006) in that they:

- are not essential in the diet of all individuals, given adequate sun exposure (Dusso et al 2005, Nowson & Margerison 2001)
- are structurally steroid derivatives (Gropper et al 2009)
- are inherently biologically inactive and require hydroxylation to produce the active form (Holick 2005b, Kemmis et al 2006)
- produce $1,25\ (OH)_2D$, which is a steroidal hormone (Dusso et al 2005)
- require VDR on cell surfaces, a member of the steroid receptor superfamily, to convey most if not all of their actions (Dusso et al 2005, Holick 2004).

These discoveries and others have precipitated a revolution in vitamin D research over the last decade (Dusso et al 2005, Holick 2004, Holick 2005b).

CHEMICAL COMPONENTS

Cholecalciferol (D_3) is considered to be the most important dietary form and is identical to the form produced in the body. Ergocalciferol (D_2) is produced by fungi and yeasts and is rare in the diet, but a common supplemental/fortificant form (Nowson & Margerison 2002). Some authors suggest that D_2 should not be classified as a nutrient, given that it has no natural place in human biology (Trang et al 1998, Vieth 2006) and, while both D_2 and D_3 were previously considered to be equipotent as supplements (FAO/WHO 2002, Nowson & Margerison 2002, Wahlqvist 2002), recent exploration of this issue points to marked discrepancies in favour of D_3 (see box). D_2 also comes under the names 1-alpha-OHD_2, calcifediol, calciferol, dihydrotachysterol (DHT), ergocalciferolum and ergosterol; D_3 may be referred to as 1-alpha-OHD_3, alfacalcidiol, calcitriol or rocaltrol (Micromedex 2003).

Quantification of any of the vitamin D forms is expressed in either International Units (IU) or micrograms. The conversion is: 1 μg = 40 IU.

Are all vitamin D forms alike?

Coincident with the recognition of 25(OH)D as the key marker of individual vitamin D status, the ability of cholecalciferol (D_3) and ergocalciferol (D_2) to increase serum levels of this marker have been compared (Trang et al 1998). Results from these studies reveal a 70% greater increase in serum 25(OH)D in response to cholecalciferol (D_3). Hypothesised reasons for this difference are based upon the distinct metabolic handling of the two different forms. D_3 demonstrates higher affinity for D binding protein (DBP), making it less likely to be excreted in bile (Armas et al 2004, Dusso et al 2005), produces more potent metabolites and is converted into 25(OH)D up to five times faster than D_2 (FSANZ 2007, Houghton & Vieth 2006, Trang et al 1998). The results of another study showed that serum 25(OH)D increases in response to D_2 supplementation were not sustained, and in fact fell below baseline values over 14 days, while the serum levels of those supplemented with D_3 continued to rise throughout the same period (Armas et al 2004). In addition to these concerns, the stability and purity of D_2 preparations are questionable (Houghton & Vieth 2006).

These findings have major ramifications for the interpretation of vitamin D research and the clinical implementation of such protocols. Every piece of vitamin D research must now be considered in the light of the supplemental form used. Clinically D_3's improved potency translates to significantly lower dose requirements, in the vicinity of 2.5–10 times less) (FSANZ 2007, Houghton & Vieth 2006), compared with a D_2-based product (Glendenning 2002).

FOOD SOURCES

Small amounts are found in fatty fish, such as herring, salmon, tuna and sardines, beef and liver, butter, eggs and fortified foods such as margarine and milk (Gropper et al 2009). Cod liver oil is also a good source. Notably, meat products also contain some 25(OH)D, which is five times more active than D_3 (Nowson & Margerison 2001); however, the vitamin D content of all animal products is dependent upon the individual animal's vitamin D status and the use of fortified feed (Mattila et al 2004). There is therefore concern that as a consequence of modern agricultural and aquacultural practices vitamin D content is in decline, as demonstrated by a recent study which revealed a 75% decrease in the vitamin D content of farmed compared to wild salmon (Lu et al 2007). Naturally occurring D_2 is found only in mushrooms.

Current vitamin D fortification practices in Australia permit the use of either D_2 or D_3 without distinction and include both mandatory fortification (edible oil spreads and table margarine) and voluntary fortification (modified and skim milks, powdered milk, yoghurt, cheese, butter, legume- and cereal-based analogue beverages) (FSANZ 2007, Nowson & Margerison 2001). Australian diet studies reveal that fortified margarine and edible oil spreads make the largest single contribution to vitamin D consumption (28–53%) (NHMRC 2006, Nowson & Margerison 2001). A recent Australian study found that average dietary consumption of vitamin D was 1.2 μg/day and that only 7.9% of this sample took vitamin D supplements (van der Mei et al 2007).

DEFICIENCY SIGNS AND SYMPTOMS

Although the traditional understanding of hypovitaminosis D revolves around its critical role in calcium metabolism, the extensive presence of VDR throughout the body is providing the impetus for further research into actions, deficiency states and therapeutic applications (Gropper et al 2009).

Primary deficiency

Unlike many other vitamins, vitamin D is not only ingested through the diet but also produced and stored in the body. As such, endogenous production, which is reliant on adequate exposure to sunlight, will greatly influence whether deficiency states develop. It has been estimated that exposing the skin to UVB radiation produces approximately 90% of the vitamin D_3 (cholecalciferol) that is bioavailable in the body. Currently, the NHMRC reports that it is almost impossible to get sufficient vitamin D from dietary sources alone, stressing the importance of UVB exposure (NHMRC 2006).

Deficiency more prevalent than once thought

Inadequate vitamin D among Australians is now recognised as a substantial concern, given the significant percentage demonstrating a combination of poor dietary intake and inadequate sun exposure, according to the 2005 position statement released by the Working Group of the Australian and New Zealand Bone and Mineral Society, Endocrine Society of Australia and Osteoporosis Australia.

Ongoing epidemiological research in Australia supports this view and has identified the wider community at risk of mild deficiency, with the results of numerous studies supporting this preposition. Using a cut-off of ≤ 50 nmol/L for serum 25(OH)D, vitamin D insufficiency has been found to affect > 40% of healthy adults in Queensland (Kimlin et al 2007, van der Mei et al 2007), > 65% Tasmanians (van der Mei et al 2007) and up to 74% of general medical inpatients (Chatfield et al 2007) — including 54% of the last group who were taking vitamin D supplements. A study of maternal and neonatal levels in Sydney revealed that 15% of mothers (at 23–32 weeks' gestation) and 11% of neonates met the criteria for overt vitamin D deficiency (≤ 25 nmol/L) (Bowyer et al 2009). These rates increase dramatically if the reference range for optimal serum 25(OH)D is raised, as has been proposed in the scientific literature (Dawson-Hughes et al 2005, Vieth 2001, Vieth 2006). One group of researchers re-analysed population data based on the proposed cut-off of ≤ 80 nmol/L (Dawson-Hughes et al 2005, Heaney 2006, Holick 2005b) and found that 70% of their sample of healthy Australians would, using this definition, be below optimal (van der Mei et al 2007).

Factors associated with lower 25(OH)D levels in Australia include:

- seasonal effects, with winter–early spring demonstrating peak incidence (Bowyer et al 2009, Chatfield et al 2007, Kimlin et al 2007, McGillivray et al 2007, van der Mei et al 2007)
- increasing latitude (van der Mei et al 2007)
- increasing skin pigmentation (Kimlin et al 2007), with one study calculating an odds ratio of 2.7 for dark skin (Bowyer et al 2009)
- non-Australian birthplace: odds ratio (OR) 2.2 (Erbas et al 2008)
- hospitalisation, and institutionalisation and age (Bruyere et al 2009).

The institutionalised elderly are of particular concern, as their exposure to sunlight is often restricted and they have an estimated twofold reduction in capacity of the skin to produce D_3 (Wilson et al 1991), compromised final conversion in the kidneys, reduced tissue response and further reductions to calcium absorption independent of these pathways (Bouillon et al 1997, FAO/WHO 2002). The increasing risk with age is clearly demonstrated by the results of a Tasmanian study, which revealed that although only 8% of 8-year-olds were considered vitamin D deficient, deficiency escalated with increasing age to peak at 85% for people aged 60 years (RACGP 2003).

At the other end of the age spectrum, a 2-year surveillance of infants presenting with vitamin-D-deficiency-related problems at the Monash Medical Centre in Clayton, Victoria, found that the 13 infants admitted to hospital all had migrant parents and were predominantly or exclusively breastfed (Pillow et al 1995). This is a dangerous combination, with dark-skinned migrants at a significantly greater risk of deficiency (Bowyer et al 2009, Erbas et al 2008), particularly women who are veiled (OR 21.7) (Bowyer et al 2009, Grover & Morley 2001, Nowson & Margerison 2002, Wigg et al 2006), and breastmilk recognised as a poor source of vitamin D (Andiran et al 2002). Australian research demonstrates that recently immigrated infants or first-generation offspring of immigrant parents, especially Indian, Middle Eastern, African and Polynesian, are a key at-risk group: 40% of infants aged 4–12 months were found to be deficient (Nozza & Rodda 2001, Robinson et al 2006) and 87% of sampled east-African children (0–17 years) living in Melbourne recorded serum 25(OH)D levels ≤ 50 nmol/L (McGillivray et al 2007).

Other populations at risk include obese individuals (Arunabh et al 2003, Blum et al 2008, Harris & Dawson-Hughes 2007), psychiatric patients (Berk et al 2007) and individuals with an intellectual disability (estimated deficiency prevalence 50–60%) (Vanlint et al 2008).

Secondary deficiency

Malabsorption states such as coeliac disease, Crohn's disease, gastrectomy, intestinal resection, chronic cholestasis, cystic fibrosis and pancreatic disorders

Clinical note — The vitamin D dilemma

Between 80% and 100% of our vitamin D needs can be met through adequate sun exposure, with dietary intake only required to meet the shortfall (Nowson & Margerison 2001, Nowson & Margerison 2002, Samanek et al 2006). Quantifying this shortfall, however, is complex and individualistic, as multiple variables influence the rate of endogenous production, such as age, season, latitude, time of day, part of body exposed to sunlight and use of sunscreen. Researchers estimate that full-body sun exposure in Australia, sufficient to induce mild erythema, is equivalent to consuming 15,000 IU orally (Working Group 2005). Hence, we have the dilemma: while the majority of public health messages continue to promote sun-protection, there is growing media coverage of the negatives associated with this and advocacy for exposure to UVB in order to prevent vitamin D deficiency (Scully et al 2008). The successful 'Slip slop slap' campaign in Australia, which encourages covering up and reduced sun exposure, appears at odds with the vitamin D message and may have put many Australians at risk of poor vitamin D status. Recent Australian research concurs with this, indicating that the public health message battle is currently being won by 'sun protection', with only 15% of surveyed Australians agreeing with the statement that 'sun protection may result in not having enough vitamin D' (Janda et al 2007).

Clearly, revision of the current public health messages regarding both vitamin D and safe sunlight exposure has been required for some time. In response, work has been undertaken to develop a message of compromise (Nowson & Margerison 2002, Working Group 2005), and the development of a 'vitamin D index', similar to a UV index, has been proposed (van der Mei et al 2007). Recent evidence from a study by Samanek et al (2006) supports the concept that safe sun exposure can yield vitamin D adequacy. Their research concluded that from October to March only 10–15 minutes of unprotected exposure to 15% of the body outside of the hours of 10 am to 3 pm was sufficient; however, during other seasons, up to 1 hour of exposure was required. In addition to this, the authors themselves acknowledge that calculations were based on existing serum values, which have been widely contested by other researchers (Gomez et al 2003). In view of some of these concerns, the new NHMRC vitamin guidelines released in 2006 are now recommending an increased AI of vitamin D, particularly for adults aged over 50 years. It also suggests varying lengths of time for sun exposure for different skin types in order to achieve adequate levels. Whether these initiatives are sufficient to prevent deficiency in the community remains to be seen.

increase the risk of deficiency (Hendler & Rorvik 2001, Kumar & Clark 2002).

The use of certain anticonvulsants and chronic administration of glucocorticoids increase the risk of vitamin D deficiency. Several rare hereditary forms of rickets develop because the body cannot process (metabolise) vitamin D normally (Beers & Berkow 2003). Chronic liver disease will obstruct the first hydroxylation reaction, and end-stage kidney disease results in negligible conversion of 25-OHD into 1,25-OHD (Kumar & Clark 2002, Micromedex 2003). One large study also demonstrated that levels of serum 25-OHD are inversely correlated with percentage of body fat and, as such, morbidly obese individuals have increased requirements (Arunabh et al 2003).

Signs and symptoms of deficiency

The previously determined serum concentrations of 25-OHD believed to be indicative of deficiency (< 20–25 nmol/L) are considered outdated (Gomez et al 2003). It is now apparent that much higher concentrations, deemed 'suboptimal' status, have deleterious effects (Dawson-Hughes et al 2005, Heaney 2006, Holick 2005b, Nowson & Margerison 2002). Indications of deficiency include:

- alopecia with dilated hair follicles and dermal cysts (Dusso et al 2005)
- anaemia, decreased bone cellularity and extramedullary erythopoiesis (Brown et al 1999)
- cardiomegaly (Dusso et al 2005, Holick 2005b)
- chronic fatigue syndrome (deficiency may be misdiagnosed as this) (Holick 2004, Schinchuk & Holick 2007)
- chronic lower back pain (Al Faraj & Al Mutairi 2003)
- excess PTH secretion and parathyroid hyperplasia
- fibromyalgia (estimated that 40–60% of patients diagnosed with this condition are actually suffering from vitamin D deficiency) (Holick 2004, Holick 2005b, Schinchuk & Holick 2007)
- hypertension (Dusso et al 2005, Forman et al 2007, Holick 2005b)
- impaired glucose-mediated insulin secretion (Brown et al 1999)
- increased risk of fracture in the elderly (not limited to vitamin D's influence on bone mass)
- increased susceptibility to mycobacterial and viral infections (Dusso et al 2005)
- peripheral vascular disease with claudication (may be misdiagnosed or confounding factor) (Holick 2005b)
- rickets and osteomalacia
- osteopenia and osteoporosis
- sarcopenia — skeletal muscle weakness and atrophy (Dusso et al 2005, Visser et al 2003)
- stunting.

Deficiency also significantly increases the risk of:

- autoimmunity, including multiple sclerosis (including increased severity of preexisting cases) (Dusso et al 2005, Holick 2004), diabetes type 1 (Holick 2006) and inflammatory bowel disease (Holick 2004)
- cancer — breast, prostate, colon and skin cancers are among the 20 different cancer types demonstrating an inverse relationship with vitamin D levels (Holick 2004)
- heart failure in CVD patients (Holick 2005b)
- non-insulin-dependent diabetes mellitus in high-risk populations — some studies (Pittas et al 2007) but not all (Reis et al 2007) show positive association
- preeclampsia — particularly if hypovitaminosis D is present at < 22 weeks (Bodnar et al 2007).

MAIN ACTIONS

Whereas vitamin D is considered a fat-soluble vitamin, its active metabolite $1,25(OH)_2D_3$ is considered to be more like a steroid hormone, because it can be produced by the body and moves through the systemic circulation to reach target tissues via receptors both at the cell membrane and at the nuclear receptor proteins. Vitamin D possesses two distinct action pathways dependent upon the site of bioactivation (Dusso et al 2005, Holick 2006). Renal hydroxylation of 25(OH)D produces $1,25(OH)_2D$, primarily responsible for its traditional endocrine actions mentioned, as well as playing a role in intestinal detoxification (Kutuzova & DeLuca 2007), healthy insulin secretion (Brown et al 1999, Dusso et al 2005, Mathieu & Badenhoop 2005) and blood pressure control, via inhibition of rennin production and blunting cardiomyocyte hypertrophy (Dusso et al 2005, Holick 2005b, Simpson et al 2007).

Extrarenal bioactivation, by immune, prostate, breast, colon, beta and skin cells, however, results in non-genomic responses characterised as autocrine rather than endocrine effects (Dusso et al 2005, Kemmis et al 2006, Holick 2006). These autocrine effects include controlling immune function (especially anti-inflammatory), cellular growth, maturation, differentiation and apoptosis (Dusso et al 2005, Kemmis et al 2006, Lips 2006, Holick 2005b) as well as photoprotection (Dixon et al 2007), explaining vitamin D's emerging role in immune function and cancer prevention.

Regulation of calcium and phosphorus levels

In conjunction with PTH, which is released under conditions of low calcium levels, vitamin D can stimulate calcium and phosphorus absorption in the intestines, reabsorption in the kidneys and release of calcium from the bones back into the blood. $1,25-(OH)_2D_3$ in turn is regulated by PTH, calcium, phosphorus and $1,25-(OH)_2D_3$ itself (Wahlqvist 2002). To achieve the maximal efficiency of vitamin D-induced intestinal calcium transport, the serum 25(OH)D concentrations must be at least 78 nmol/L (30 ng/mL). In deficiency, intestinal absorption of calcium can be halved in adults (Holick 2004).

Modelling and remodelling of bone

Besides influencing bone by maintaining calcium and phosphorus homeostasis, vitamin D may also contribute to bone health in other ways.

One pathway involves binding of $1,25\ (OH)_2D_3$ to DNA to promote transcription of specific mRNA, which codes for osteocalcin. Osteocalcin

is then secreted by the osteoblasts, which bind calcium in new bone (Gropper et al 2009). Vitamin D also appears to play a role in oestrogen biosynthesis by increasing expression of the aromatase enzyme gene. It has demonstrated a synergistic effect in select tissues with the phyto-oestrogen genistein, with co-administration leading to a prolonged half-life of active vitamin D (Harkness & Bonny 2005, Swami et al 2005).

Cell differentiation, proliferation and growth

Some of the actions already described are the result of the vitamin's capacity to affect cell differentiation, proliferation and growth in many tissues (e.g. differentiation of stem cells into osteoclasts to facilitate bone resorption). Alternatively, 1,25-$(OH)_2D_3$ can inhibit proliferation in many cells, including lymphocytes, keratinocytes, mammary, cardiac and both skeletal and smooth muscle cells. This ability has led to its investigation as a treatment for proliferative disorders such as cancer (Brown et al 1999, Gropper et al 2009, Kohlmeier 2003).

Reduction of PTH and regulation of growth of the parathyroid gland

Although PTH regulates the levels of 1,25-$(OH)_2D$, its secretion is regulated by vitamin D, calcium and phosphorus. In deficiency, hypersecretion of this hormone can cause excessive growth of the parathyroid gland and secondary hyperparathyroidism (Brown et al 1999).

Immunomodulation

Vitamin D enhances the immune system's response to both bacterial and viral agents (Grant 2008c), primarily through promoting differentiation and activity of the macrophages, which means that immune responses can be tailored through the appropriate cell response (Brown et al 1999) but also through the induction of cathelicidin (Maalouf 2008). Vitamin D influences the cytokine production of immune cells, suppressing the release of IL-2, IFN-gamma and TNF-alpha, products of the Th-1 line of cells, thereby reducing the propensity for a range of autoimmune conditions (Thien et al 2005). This reflects its propensity for inhibiting adaptive immunity while potentiating the innate response (Bikle 2008). There is speculation that through this mechanism, vitamin D will promote a Th-2 dominance and may predispose to the atopic diathesis. Supporting evidence comes from two studies that reveal supplementation with vitamin D in early life to be a potential precipitator of allergic disease (Hypponen et al 2001); however, in other scenarios (e.g. autoimmunity) this effect would be considered to be therapeutic (Smolders et al 2008).

OTHER ACTIONS

Our current understanding of the role of vitamin D appears to be only part of the picture. Ongoing discovery of previously unidentified receptors on tissues continues to broaden our understanding of its diverse effects.

Haematopoietic tissues

Vitamin D appears to exert an effect on erythopoiesis and bone cellularity through unknown mechanisms. It has also been shown to inhibit clonal cell proliferation in some leukaemia lines and to promote differentiation (Brown et al 1999).

Muscle

Vitamin D maintains muscle strength and has an effect in skeletal muscle and myocardial function. Although it has been established that skeletal muscles have receptors for vitamin D, the specific actions of this steroid on muscle are largely unknown. Recently a link between fibromyalgia and vitamin D deficiency has been suggested, 40–60% of cases presenting with generalised muscle weakness and pain being estimated as undiagnosed hypovitaminosis (Holick 2004). Through unidentified mechanisms vitamin D exerts a direct effect on the myocardium: 1,25-$(OH)_2D_3$ controls hypertrophy in cardiac monocytes and, together with 25-OHD, improves the left ventricular function in patients with cardiomyopathies (Brown et al 1999).

Pancreas

Vitamin D is essential for normal insulin secretion, as demonstrated in both animals and humans, and vitamin D receptors have been found in pancreatic beta cells, whose function improves following vitamin D repletion (Alemzadeh et al 2008, Mathieu & Badenhoop 2005, Palomer et al 2008). Enhanced insulin synthesis may be due to vitamin D's role in controlling intracellular calcium flux in islet cells which facilitates conversion of proinsulin to insulin, exocytosis of insulin and beta cell glycolysis (Brown et al 1999, Palomer et al 2008). Vitamin D also modulates insulin receptor gene expression (Palomer et al 2008).

Brain

Evidence is emerging about the specific role of vitamin D in the brain. Information to date implicates 1,25$(OH)_2D$ in the biosynthesis of neurotrophic factors, contribution to brain detoxification pathways with increased glutathione and reduced nitric oxide, neuroprotective effects, induction of glioma cell death and involvement in neurotransmitter synthesis, including acetylcholine and the catecholamines (Garcion et al 2002). The vitamin D receptor (VDR) and 1-alpha-hydroxylase activity has been demonstrated in specific brain regions (e.g. the hypothalamus), implying a potential role for vitamin D as a neuroactive hormone (Berk et al 2007, Obradovic et al 2006, Vieth et al 2004). There is also increasing evidence of vitamin D's modulation of several neurotransmitters, such as acetylcholine, catecholamines, serotonin (Jorde et al 2006, Obradovic et al 2006). Preliminary studies in rats have demonstrated an anti-epileptic action (Kalueff & Tuohimaa 2005). Tentative links are being made between the aetiology/pathophysiology of Parkinson's disease and poor vitamin D status (Johnson 2001, Kim et al 2005).

CLINICAL USE

Vitamin D is administered using various routes and can be prescribed as either a supplement or a drug. This review will focus on oral supplementation of D_2 or D_3 only and will not cover the variety of analogues that continue to be extensively studied. For many conditions that appear to require high doses, the race is on to develop and trial pharmaceutical analogues that retain, in particular, the antiproliferative nature of the vitamin, but are low-calcaemic in order to minimise the associated toxicity seen at such doses.

Deficiency states

Frank vitamin D deficiency in infancy or childhood produces rickets, which results from reduced sun exposure, deficient diet or metabolic or malabsorptive diseases. Vitamin D deficiency results in inadequate calcium and phosphorus levels for bone mineralisation (Beers & Berkow 2003). Diagnosis is confirmed with X-ray and serum assay of 25(OH)D. When occurring in adults, it is called osteomalacia, and its first presentation is often as chronic lower back pain (Al Faraj & Al Mutairi 2003).

Defective vitamin D metabolism may be another cause, and consequently deficiency will not respond to standard oral treatment. In this situation, extremely high doses may be required, which should be monitored carefully for toxicity (Beers & Berkow 2003).

Pregnancy and lactation supplementation

Vitamin D appears to be critical both to the musculoskeletal and neurological growth and to the development of the infant. A recent Australian study investigated the well-documented seasonal variation in birth weight to determine the parameters of anthropometric changes associated with this seasonal variation (McGrath et al 2005). Comparison of over 350,000 mean monthly birth weights of neonates at more than 37 weeks' gestation revealed that overall size, length, head size and skinfold thickness all display seasonal variation, but in particular greater limb length occurred with winter/spring births. Earlier animal studies imply that this may be a consequence of hypertrophy of the cartilage growth plates due to prenatal hypovitaminosis D (McGrath et al 2005).

Whether pregnant women require additional supplementation has been investigated in some studies. The Cochrane Controlled Trials Register has assessed only two trials, producing inconsistent results (Mahomed & Gulmezoglu 2000). However, trials involving more than 500 women conducted by Marya et al (1981, 1987), not included in the Cochrane Register review, have demonstrated statistically significant increased fetal birth weight, reduced prevalence of hypocalcaemia and hypophosphataemia, detected in both maternal and cord blood, and reduced blood pressure in non-toxaemic women. Additional evidence suggests a preventative role for a range of autoimmune conditions in the offspring when prenatal vitamin D levels are adequate (Holick 2004).

There is greater consensus regarding the need for vitamin D supplementation during lactation; breast milk is recognised as a poor source of this vitamin and infants are largely dependent on stored vitamin D acquired in utero (Andiran et al 2002).

Children

The optimal regime in relation to both route and dose of vitamin D for at-risk children remains controversial and is based on studies of limited size (Huh & Gordon 2008). The most common recommendation for infants is to supplement with D_2 or D_3 at 1–2000 IU/day and up to 4000 IU/day in children older than 1 year.

Treatment of deficiencies secondary to malabsorptive syndromes

Numerous studies have confirmed a high prevalence (25–75%) of hypovitaminosis D in patients with coeliac disease, Crohn's disease, small bowel resection or cystic fibrosis. A positive correlation between low vitamin D status and clinical consequences, such as reduced bone mineral density (BMD) and osteopenia, has been demonstrated in most studies. Interestingly, trials investigating the benefits of oral vitamin D supplements (400–800 IU/day) found limited success in patients. Owing to the theoretical advantage of supplementation in conditions associated with poor nutrient absorption, larger trials involving higher doses or different forms are expected to determine the most effective treatment (Buchman 1999, Congden et al 1981, Hanly et al 1985, Hoffmann & Zeitz 2000, Jahnsen et al 2002). A study of children with cystic fibrosis demonstrated 25(OH)D levels that were consistently > 50 nmol/L with an average dose of 1405 IU/day.

Cancer

In the 1930s it was reported that US navy personnel exposed to high-level UVB showed higher rates of skin cancer but lower rates of cancer malignancies (Giovanucci 2008, Grant 2008a). WHO data from as early as 1955 have demonstrated latitudinal gradients in cancer mortality rates for breast, colon, lung, prostate, rectal and renal cancer (Grant 2008a); however, the hypothesis linking UVB, vitamin D and cancer was not formally proposed until 1980. Since this time, ongoing epidemiological evidence has demonstrated in both single and multiple country studies that there is increasing cancer incidence or mortality with increasing distance from the equator (Garland et al 1999, Grant 2008a). Both advancing age and ethnicity have also been positively correlated with these cancers and this has been similarly explained in relation to reduced UVB exposure. Further epidemiological support comes from the inverse relationship between prospective serum 25(OH)D levels and cancer risk, season of cancer diagnosis and survival time and lower rates of cancer in high fish-consuming countries such as Iceland and Japan (Giovanucci 2008, Grant 2008a). Following on from this, in 2002 Grant identified 14 cancers for which there was strong evidence to support vitamin D sensitivity, including breast, colon, ovarian, prostate and rectal forms.

More recent evidence from an interventional study of calcium (1400–1500 mg/day), alone or with vitamin D_3 (1100 IU/day) versus a placebo over 4 years supports a chemoprotective role for vitamin D (Lappe et al 2007). The study, involving 1179 women > 55 years old, was primarily designed to assess reductions in fracture incidence, but upon further analysis also demonstrated significant risk reduction (RR 0.40) for all cancer incidence in the combined calcium and vitamin D group. When the analysis was restricted to those cancers diagnosed only after the first year of treatment, the RR became 0.23. While the group receiving calcium alone also demonstrated a reduced risk, the researchers speculate that this may not be robust and conclude that vitamin D is the key variable in reduced incidence of all cancer. Given the ability of vitamin D to inhibit abnormal proliferation, facilitate apoptosis, attenuate growth signals and reduce angiogenesis around tumours, its chemoprotective potential continues to be enthusiastically investigated through both in vitro studies and RCTs (Giovanucci 2008, Grant 2008a). Risk reduction via protection against viral infections has also recently been hypothesised (Grant 2008b).

Colorectal cancer and prevention of adenomatous polyps

Evidence of vitamin D's chemoprotective effect is strongest in relation to colorectal cancer (Giovanucci 2008) and comes from several different lines of investigation (Garland et al 1991, Giovanucci 2008, Grant & Garland 2004, Holt et al 2002, Holt 2008, Theodoratou et al 2008). A 2004 review of more than 20 epidemiological studies of vitamin D and colorectal cancer concluded that the overwhelming majority of studies have demonstrated an inverse relationship between dietary intake, serum 25(OH)D and incidence (Garland et al 2004). An estimate of daily requirements needed for prevention has been formulated using the data from the studies, suggesting that an oral intake of > 1000 IU/day of vitamin D or serum 25(OH)D levels of > 33 ng/mL (82 nmol/L) could reduce the risk of colorectal cancer by as much as 50%. Most intervention studies to date, however, have focused on calcium supplementation. Interestingly, some of these show calcium's protective effect against recurrent adenomas is largely restricted to individuals with baseline serum 25(OH)D above the median (≥ 29 ng/mL). These data, together with more recent findings (Mizoue et al 2008), strongly point to a synergism between calcium and vitamin D for colorectal cancer and recurring adenoma risk reduction (Grau et al 2003, Holt 2008, Oh et al 2007, Theodoratou et al 2008). An often-cited negative finding comes from the Women's Health Initiative (WHI), in which women supplemented with 1000 mg calcium and 400 IU vitamin D per day failed to demonstrate reduced cancer rates; however, several authors have published major criticisms of the study that include the inadequate dose of vitamin D administered and the time frame (Giovanucci 2008, Grant 2008a, Holt 2008). Re-analysis of the WHI findings has also elucidated oestrogen's critical modifying effect upon both nutrients, whereby higher oestrogen levels of both menstruating and postmenopausal women taking HRT negate calcium's otherwise protective effect (Ding et al 2008). Explanations for this phenomenon include competitive binding between vitamin D and oestrogen (Ding et al 2008, Oh et al 2007).

Current evidence for a combined protective role of calcium, either dietary or supplemental, and vitamin D, particularly in men and postmenopausal women not taking HRT, is strong and further elucidation of the independent and combined effects of these nutrients will assist in the development of preventative protocols.

Prostate

Vitamin D's relationship to cancer is least clear with respect to prostate cancer, with inconsistent findings from numerous studies (Giovanucci 2008, Li et al 2007, Mucci & Spiegelman 2008). Most recently, the belief that increased calcium, dairy consumption and vitamin D levels could increase risk has dominated, with epidemiological evidence from a number of substantial studies, including the Helsinki Heart Study involving 19,000 men. This study showed that increased levels of circulating $1,25(OH)_2D_3$ and low levels of 25(OH)D are inversely associated with prostate cancer, in both incidence and aggressiveness, and are associated with an earlier age of onset (Chen & Holick 2003, Mucci & Spiegelman 2008). However, evidence of the potentially protective effects of increased serum 25(OH)D and $1,25(OH)_2D$ continue to emerge (Li et al 2007), while more comprehensive investigations of the relationship between dietary vitamin D intake and risk fail to show any effect (Huncharek et al 2008), largely due to globally poor intakes. Several explanations for these contrasting findings have been proposed, including that vitamin D status many years prior to diagnosis may be more predictive and relevant than levels just before or following diagnosis (Giovanucci 2008, Mucci & Speigelman 2008).

Experimental research with vitamin D has produced interesting results. Prostate cancer cells in vitro respond to vitamin D_3 with reduced proliferation, increased differentiation and apoptosis. More recently, reduced activity of the 1-alpha-hydroxylase enzyme in cancerous prostate cells when compared to healthy prostate tissue was discovered, resulting in a reduced ability to convert vitamin D to its active form. Therefore, prostates with cancer display partial resistance to the tumour-suppressing activity of $1,25\text{-}(OH)_2D_3$ (Ma et al 2004). Clinical trials using supplemental vitamin D at various stages of prostate cancer have yielded inconsistent results (Miller 1999).

Breast

Normal breast cells produce $1,25(OH)_2D$, which in turn may contribute to healthy mammary function, inducing differentiation, inhibiting proliferation and modulating immune responses (Perez-Lopez 2008). Vitamin D receptors in mammary tissue have also been shown to oppose oestrogen-driven proliferation of cells (Welsh et al 2003). In addition,

there is growing epidemiological evidence to suggest an inverse association between vitamin D and breast cancer (Grant 2006, Grant 2008c, Mohr et al 2008, Perez-Lopez 2008), with increasing UVB exposure reported to produce a RR of between 0.67 and 0.85 (Perez-Lopez 2008). One study that involved 179 breast cancer patients and 179 controls assessed vitamin D status of patients and polymorphisms of vitamin D, and identified an inverse relationship, possibly as high as 7-fold, between 25(OH)D levels and breast cancer risk (Lowe et al 2005). Interestingly, from a population-based case control study in Ontario, there is evidence to suggest that sun exposure between the ages of 10 and 19 years is particularly protective against subsequent breast cancer diagnoses (Perez-Lopez 2008). This implies that vitamin D status may be especially important during breast development.

A more recent investigation of the effect of UVB exposure on breast cancer incidence in 107 countries also confirmed that increased UVB exposure is independently protective, with age-standardised incidence rates substantially higher at latitudes distant from the equator (Mohr et al 2008). The same study demonstrated that the protective effect was evident at serum levels above 22 ng/mL. Another study revealed that women with serum 25(OH)D ≥ 50 ng/mL halve their risk of breast cancer compared to those below this cut-off level (Perez-Lopez 2008).

A recent large meta-analysis of dietary studies initially failed to find a relationship between vitamin D intake and breast cancer risk. Restricting studies to only those with intakes > 400 IU/day, however, revealed a trend towards risk reduction with increasing vitamin D intake (RR 0.92) (Gissel 2008).

Type 1 diabetes mellitus (T1DM)

Vitamin D deficiency has been linked to both types of diabetes mellitus, but the largest volume of evidence relates to an inverse association between prenatal and infant vitamin D levels and a child's overall risk of developing T1DM. International epidemiological data highlight a marked geographical pattern of increasing incidence with increasing latitudes, together with significantly greater rates of diagnosis in autumn and winter (Svensson et al 2008, Zipitis & Akobeng 2008). In addition to this, assessment of T1DM patients reveals significantly lower 25(OH)D than age-matched controls. Given that the beta-cell destruction of T1DM frequently begins in infancy, with diagnosis typically occurring when 80% of cells have already been destroyed, much focus has been placed on the environmental and nutritional influences in early life as potential aetiological factors.

One birth cohort study published in *Lancet* in 2001 involved the offspring of 12,055 pregnant Finnish women who gave birth in 1966. The families were assessed for vitamin D supplementation in the infant's first year of life and then the child was followed until 31 years of age to account for subsequent diagnoses of T1DM. It was shown that treatment of children with 2000 IU/day vitamin D from 1 year of age decreased the risk of developing the disease by 80% through the next 20 years; furthermore, children from the same cohort who were vitamin D-deficient at 1 year old had a four-fold increased risk of developing T1DM (Hypponen et al 2001). Similar findings have been demonstrated in animal models, with pretreatment with $1,25(OH)_2D$ being effective in mitigating or preventing the onset of T1DM (Palomer et al 2008).

A case control study conducted in Norway that involved 545 Norwegian children up to 15 years old with T1DM retrospectively assessed their cod liver oil and vitamin D use from birth to 12 months old. Children who had been given cod liver oil five times a week had a 26% lower incidence of the disease, whereas other forms of vitamin D appeared to bear no relationship (Stene & Joner 2003). Although this does not adequately assess vitamin D as a sole treatment agent and is not conclusive, it adds to the growing body of evidence implicating vitamin D in a preventative role against diabetes.

A recent meta-analysis of five studies of vitamin D supplementation in infancy, including the above two, concluded that supplementation during an infant's first year appears to be associated with a significant risk reduction for the development of T1DM later in life (OR 0.71) (Zipitis & Akobeng 2008). Current evidence points to the superiority of cod liver oil as a delivery form, but a lack of specific detail in many of the studies means that optimal dose, duration of supplementation and timing can not currently be elucidated.

Type 2 diabetes mellitus (T2DM)

Epidemiological studies suggest that vitamin D deficiency places some populations (e.g. non-Hispanic blacks) at a higher risk of insulin resistance, impaired glucose homeostasis and metabolic syndrome (Palomer et al 2008). The mechanisms for this effect remain speculative, including suppression of parathyroid hormone (PTH), reducing calcium influx and therefore limiting lipogenesis etc. Other theories relate to vitamin D's immunomodulatory actions. A range of elevated inflammatory markers have been identified to predate the onset of T2DM and many of these appear to be downregulated by vitamin D, but direct evidence of this pathogenetic path is currently lacking (Palomer et al 2008). The relationship between diabetes and vitamin D, however, is likely to be a bidirectional one, with low levels of functioning insulin impairing bioactivation of vitamin D, and poor vitamin D status impeding correct insulin release and function.

Consistent evidence of an inverse relationship between serum 25(OH)D and adiposity highlights another domain of potential overlap between hypovitaminosis D and T2DM (Alemzadeh et al 2008, Palomer et al 2008). Consequently, vitamin D deficiency is common in T2DM patients (Sugden et al 2008). One study revealed that three-quarters of obese adolescents had levels < 50 nmol/L, with a positive correlation between poor vitamin D status and glucose dysregulation (Alemzadeh et al 2008), while 49% adult T2DM patients in another study demonstrated vitamin D deficiency (Sugden et al

2008). A recent meta-analysis concurs with these findings, while also adding calcium to the equation; it calculates an OR of 0.82 for incident T2DM among individuals with low vitamin D status, calcium or dairy intake (Pittas et al 2007).

Vitamin D supplementation in patients with mild T2DM and in non-diabetic patients with vitamin D deficiency can improve insulin secretion in response to oral glucose loads, but it is ineffective in patients with established or severe T2DM (Palomer et al 2008). In one clinical trial, 1332 IU/day oral vitamin D was administered for 1 month to 10 adult women with T2DM. Corresponding changes were observed in first-phase insulin secretion (34.3% increase) and serum 25(OH)D levels. Improvements observed in second-phase insulin secretion and insulin resistance were deemed non-significant (Borissova et al 2003). A more recent pilot study employed a single high dose of D_2 (100,000 IU) to vitamin-D-deficient T2DM patients; this resulted in improved endothelial function, as evidenced by a highly significant reduction in systolic blood pressure. The proposed mechanisms for this effect are many and varied but remain hypothetical at this time (Sugden et al 2008). IV administration of vitamin D to patients with gestational diabetes produces a transient reduction in both fasting glucose and insulin, suggesting improved insulin sensitivity rather than secretion (Palomer et al 2008).

It is important to note that single high-dose vitamin D actually increases blood glucose levels in patients with diabetes (Palomer et al 2008).

Hypoparathyroidism

Vitamin D in combination with calcium has established benefits in the treatment of hypoparathyroidism, by promoting homeostasis of calcium, phosphorus, 25 (OH)D and PTH levels (Mimouni et al 1986).

Secondary hyperparathyroidism

In a controlled study of 100 postmenopausal women with confirmed vitamin D deficiency (< 18 nmol), supplementation with combination calcium and low-dose vitamin D showed more significant reductions in PTH levels over the 90-day trial period than supplementation with calcium alone (Deroisy et al 2002).

Hypophosphataemia

A combination of high-dose vitamin D and phosphorus results in improved phosphorus and calcium balance in these patients (Lyles et al 1982).

Osteoporosis and fracture prevention

Both serum 25(OH)D and $1,25(OH)_2D$ levels are low in osteoporotic patients (Cranney et al 2008, Hunter et al 2000, Wilson et al 1991); however, conclusions regarding improvement of bone health with vitamin D supplementation alone have been mixed and largely hampered by methodological issues (e.g. accurate vitamin D assessment, accounting and discriminating between different vitamin D sources, extricating effects of vitamin D from those of calcium) (Cranney et al 2008). A 2008 systematic review that included 17 RCTs of either D_2 or D_3 supplementation (300–2000 IU/day) in postmenopausal women or older men has found consistent evidence of a protective effect of D_3 at doses of ≥ 700 IU/day in combination with calcium (500–1200 mg/day) (Cranney et al 2008). Notably, however, vitamin D at these doses provided no additional benefits in black populations. A recent meta-analysis of 29 RCTs conducted in 63,897 individuals ≥ 50 years over an average of 3.5 years also concluded that calcium alone (≥ 1200 mg/day) or in combination with vitamin D (≥ 800 IU/day) reduced the risk of fracture by 12–24%, and reduced bone loss by 0.54% at the hip and 1.19% at the spine (Tang et al 2007). The greatest improvements were noted specifically in the elderly, institutionalised, underweight and calcium-deficient. In addition, a recent Australian trial that investigated the administration to 120 women aged 70–80 years of 1200 mg/day of calcium alone or in combination with 1000 IU vitamin D over 5 years yielded beneficial effects on bone mineral density (BMD) and bone turnover markers for both treatment groups, with evidence of more sustained improvements in those also taking vitamin D (Zhu et al 2008). Another recent study comparing the combined effects of calcium (500 mg/day) with either oral vitamin D_2 (700 IU/day) or calcitriol over 3 years demonstrated a protective effect of vitamin D_2 on the spine but not on the hip (Zofkova & Hill 2007).

Serum 25(OH)D levels in postmenopausal women are inversely associated with fracture risk, independent of number of falls, physical functionality, frailty and other associated risks (Cauley et al 2008). These data reveal that individuals with baseline serum levels < 47.5 nmol/L have an increased risk of hip fracture rate over the next 7 years of 1.71 compared to those with values > 70.7 nmol/L. Other studies of similar design concur with these results, while producing different cut-off values. Studies investigating vitamin D supplementation for fracture prevention in osteoporosis have produced some positive results. In the context of adequate or supplemented calcium, a 60% reduction in the incidence of peripheral fractures was observed by Cosman (700–800 IU/day), with a 40% reduction in hip fracture incidence specifically (Cosman 2005). A recent systematic review of 15 RCTs involving mostly D_3 supplementation (300–800 IU/day) found a non-significant reduction in fractures; however, methodological limitations, including the relatively low dose, could be a confounding issue (Cranney et al 2008).

One study has investigated the BMD effects of co-supplementing silicon with calcium and vitamin D. In a recent RCT of 136 predominantly postmenopausal osteopenic women, 1000 mg calcium, 20 mcg vitamin D and either 3 mg, 6 mg or 12 mg silicon in the form of orthosilicic acid was administered daily for 12 months to the treatment group. These subjects demonstrated significantly greater type I collagen, indicative of increased bone synthesis, compared to those receiving the placebo (Spector et al 2008). There was also a trend of decreasing resorption with increasing silicon dose.

The mechanisms behind vitamin D's bone actions are not limited to the suppression of PTH and improved calcium balance alone; evidence also exists of direct inhibition of bone resorption and reduced inflammatory markers. There is also speculation regarding vitamin D's potential positive effects on lean body mass, which would then convey an anabolic effect via increased mechanical load (Cauley et al 2008, Zofkova & Hill 2007).

Reducing falls in the elderly

Poor vitamin D status (e.g. low serum 25(OH)D, compromised VDR numbers or binding affinity, colder seasons) is independently associated with an increased risk of falling in the elderly, particularly in those aged 65–75 years (Prince et al 2008, Richy et al 2008, Snijder et al 2006) and in some studies with poorer physical performance generally (Brunner et al 2008). A 2004 review of double-blind RCTs of vitamin D in elderly populations concluded that vitamin D supplementation reduced the risk of falling by more than 20%. The results were significant only in women and appeared to be independent of calcium administration, type of vitamin D and duration of therapy (Bischoff-Ferrari et al 2006). More recent research has suggested an even greater effect, but the degree of risk reduction varies between studies. According to a double-blind randomised trial involving 64 institutionalised elderly women (age range: 65–97 years; mean 25(OH)D levels: 16.4 ng/mL), treatment with 1200 mg/day calcium plus 800 IU/day D_3 over 3 months reduced the rate of falls by 60% compared with calcium supplementation alone (Bischoff-Ferrari et al 2006). An Australian study of community-based women aged 70–90 years with baseline serum 25(OH)D < 24 ng/mL found that D_2 (1000 IU/day) in combination with 1000 mg calcium citrate over 1 year reduced falls by 19% (Prince et al 2008). An interesting finding was the marked seasonal variation in efficacy, with vitamin D's protective effect evident in winter/spring (months exhibiting increased risk of falls generally) but not in summer/autumn. This has been attributed to the decline in serum 25(OH)D during these months and has also been postulated as an explanation for the lack of effect seen in some larger long-term studies. The researchers also concluded that a serum level of < 24 ng/mL is predictive of individuals who may benefit from vitamin D supplementation in this context.

In 2007 a pilot study of an osteopenic/porotic elderly female population ($\geq$ 65 years) investigated the possible additional clinical benefits of 3 months' exercise training and increased protein intake on top of year-long calcium and vitamin D supplementation (500–1000 mg/day and 400–800 IU/day, respectively) (Swanenburg et al 2007). Although the number of falls reduced dramatically in both groups, the group undertaking exercise training demonstrated greater and more sustained risk reduction (e.g. 100% at 6 months versus 40%). This multipronged approach appears promising and warrants further investigation. A recent systematic review funded by the US Office of Dietary Supplements of the National Institute of Health and the Agency for Healthcare Research and Quality included 14 RCTs of vitamin D for fall prevention and concluded that there was consistent evidence of benefit (OR 0.89) (Cranney et al 2008).

As a result of the accumulating evidence, routine vitamin D administration has been recommended for those institutionalised or housebound elderly who are already at risk of deficiency (Sambrook & Eisman 2002). The findings of an Australian study, however, suggest there are a significant number of community-dwelling elderly with sufficiently low vitamin D status who might also benefit from routine vitamin D (Prince et al 2008). One additional consideration is the best delivery form, with a recent comparative meta-analysis demonstrating superior results from vitamin D analogues, e.g. alfacalcidol and calcitriol, when compared to oral vitamin D (Richy et al 2008). These analogues, which override renal regulation of vitamin D bioactivation, may be particularly indicated in individuals who take high-dose glucocorticoids, exhibit impaired renal function or chronic inflammation, or who have T1DM.

Anticonvulsant-induced osteomalacia

Preliminary evidence has shown vitamin D to be an effective treatment for this condition; however, much emphasis has been placed on establishing the most superior form of D, D_2 or D_3, as they exhibit important metabolic differences in these patients (Hartwell et al 1989, Tjellesen et al 1985, 1986). Results of the RCTs to date suggest that D_2 may be the most effective form in the restoration of bone mineral content in patients on anticonvulsant treatment (Tjellesen et al 1985).

Hepatic and renal osteodystrophy

Both chronic liver disease and those conditions exhibiting end-stage renal disease result in compromised hydroxylation of vitamin D to produce its active metabolite. It has been reported that 50% of patients with chronic liver disease, especially those with primary or secondary biliary cirrhosis, present with associated osteodystrophy. This frequently leads to a vitamin D deficiency and manifests most commonly as metabolic bone disorders, hypocalcaemia and secondary hyperparathyroidism (Wills & Savory 1984). The resultant hypovitaminosis D can result in bone loss, cardiovascular disease, immune suppression and increased mortality in patients with end-stage kidney failure (Andress 2006). Consequently, correction of this deficiency has been one of many first-line treatments in these situations.

Although vitamin D_2 supplementation in combination with calcium, phosphorus and magnesium (where indicated) has shown some success in those patients with hepatic osteodystrophy (Compston et al 1979, Long & Wills 1978), recent trials and emerging research implicate other factors in the aetiology of these sequelae (Klein et al 2002, Suzuki et al 1998). As such, therapy with D_2 may need to be reviewed.

The treatment of renal osteodystrophy is reliant upon only the active forms or analogues of vitamin D, and natural supplementation is ineffective

because of the inability to convert these precursors into 1,25-alpha-$(OH)_2$D (Kim & Sprague 2002).

Localised and systemic scleroderma

Although patients suffering from scleroderma do not show compromised D synthesis (Matsuoka et al 1991), vitamin D_3 has been investigated as a therapeutic agent to moderate the excessive proliferation and collagen production typically seen in this condition. An in vitro study assessing the action of vitamin D_3 on the behaviour of affected fibroblasts has confirmed a non-selective antiproliferative action (Boelsma et al 1995).

To date, clinical studies have produced mixed results. Clinical trials focusing on generalised scleroderma have involved small numbers and produced promising results, such as increased joint mobility, reduced induration and increased extensibility of the skin, with benefits lasting at least 1 year after discontinuation of treatment (Caca-Biljanovska et al 1999, Hulshof et al 1994). However, the largest RCT involving 27 patients (the majority of whom suffered a localised condition) found that treatment over 9 months with a similar dose of D_3 failed to produce any significant changes in any of the assessment criteria (Hulshof et al 2000). These results suggest that different therapies may be required for the two conditions; however, larger controlled studies are needed to confirm those positive results from the preliminary open trials.

Prevention and treatment of infections

The potential immune-enhancing effect of vitamin D was first described indirectly in 1849, when cod liver oil was attributed with being one of the most efficacious agents in the treatment of pulmonary tuberculosis (PTB) (Maalouf 2008). Remarkably, in spite of mounting evidence regarding the vast and potent immunomodulatory effects of vitamin D, the evidence supporting its use in the prevention and treatment of infections has not progressed substantially and the small number of in vivo studies conducted in this area possess marked methodological weaknesses. The most robust evidence to date comes from a small study of 67 PTB patients, who received 10,000 IU/day in addition to standard antimycobacterial treatment and showed higher rates of sputum conversion and radiological improvement as a result. Several post-hoc analyses of vitamin D supplementation studies using other primary outcomes (e.g. fracture) have revealed trends of decreasing infections, colds and flu for those individuals taking a minimum of 800 IU/day (Grant 2008b, Maalouf 2008).

Depression

Patients with primary hyperparathyroidism, which secondarily impedes the bioactivation of vitamin D and raises serum calcium, frequently present with depressive disorders that normalise following successful PTH lowering (Hoogendijk et al 2008). Rodents deficient in VDR demonstrate mood abnormalities that include increased anxiety (Hoogendijk et al 2008, Jorde et al 2006, Obradovic et al 2006) and the presence of both VDR and 1-alpha-hydroxylase activity in specific brain regions (e.g. hypothalamus) implies a potential role for vitamin D as a neuroactive hormone (Berk et al 2007, Obradovic et al 2006, Vieth et al 2004). There is also increasing evidence of vitamin D's modulation of several neurotransmitters, such as acetylcholine, catecholamines and serotonin (Jorde et al 2006, Obradovic et al 2006). Yet in spite of such strong theoretical underpinning, concerted research into the links between vitamin D and mood have only recently begun in earnest.

Recent epidemiological data reveal a strong independent inverse relationship between serum 25(OH)D and both depression scores and cognitive impairment in elderly subjects (Hoogendijk et al 2008, Johnson et al 2008, Wilkins et al 2006), premenstrual syndrome, seasonal affective disorder (SAD), non-specific mood disorder and major depressive disorder in women (Murphy & Wagner 2008), depression and anxiety in fibromyalgia patients (Armstrong et al 2007), depression rating scores on the Beck Depression Inventory in overweight and obese patients (Jorde et al 2008), and significantly lower vitamin D levels in patients with uni- and bipolar depression compared with matched controls (Berk et al 2007).

Initial interventional studies of vitamin D supplementation produced mixed findings in depression, SAD and general wellbeing; however, notably low doses were used (400 IU/day over short durations and in small samples), which may partly explain this lack of effect in some studies (Berk et al 2007, Hoogendijk et al 2008, Lansdowne & Provost 1998). More recent study designs have attempted to account for such shortcomings and have produced more consistent results (Jorde et al 2008, Vieth et al 2004). In two studies thyroid outpatients with low vitamin D status during summer received either 600 IU or 4000 IU/day over the following 6 months (a placebo treatment was deemed unethical, given confirmation of hypovitaminosis D of all subjects at baseline). When vitamin D status and wellbeing questionnaires were repeated the following winter, improvements in mood and self-reported health were noted, particularly in those patients taking 4000 IU/day and those with the lowest serum concentrations at baseline. Another study of 441 overweight and obese individuals, only some of whom had vitamin D deficiency, found that supplementation with either 40,000 IU/week or 20,000 IU per week in combination with 500 mg/day calcium over 1 year produced significant reductions in depression rating scores (Jorde et al 2008). The greatest effects were evident in those with higher depression scores at baseline and were independent of both BMI and initial serum 25(OH)D values. Another recent study of elderly women supplemented with 800 IU/day and 1000 mg/day calcium, however, failed to produce improvements on mental health scores (Dumville et al 2006).

Vieth et al (2004) comment that previous studies have suggested gender-specific mood effects of vitamin D, with women being more susceptible to seasonally dependent mood lability and more responsive to supplementation. They also identify

many potential modulating influences upon vitamin D's mood effects which future researchers must take into consideration in addition to baseline 25(OH)D: season, dose, duration, age and sex. More well-designed research is needed in this area to clarify the real therapeutic potential of vitamin D in depressed mood.

OTHER USES

Multiple sclerosis (MS)

There is reasonably strong ecologic and case–control evidence that improved vitamin D status reduces the risk of multiple sclerosis (Grant 2006, Kampman & Brustad 2008, Niino et al 2008, Smolders et al 2008). A variety of observational studies illustrate a relationship between MS incidence and geographical location, with very low prevalence in the equatorial regions and increasing risk with increasing latitude in both hemispheres. Other demonstrated associations with MS incidence include the level of outdoor activity in adolescents and risk of onset later in life, while there is evidence of lower 25(OH)D levels in newly diagnosed patients when compared to controls and in relapsing patients compared to those in remission (Kampman & Brustad 2008, Niino et al 2008, Smolders et al 2008). Evidence is more mixed regarding VDR polymorphisms, month of birth and season of diagnosis. In spite of these findings, strong evidence linking vitamin D to modulation of MS is currently lacking. A very limited number of interventional studies using vitamin D also leave us without a firm conclusion. Some studies, including the Nurses Health Study, point towards a protective effect in the years following regular supplement use, but the effects of vitamin D are difficult to extricate from other supplemented nutrients. In an open and uncontrolled study of 39 MS patients treated with 1000 IU/day for 6 months, changes in inflammatory markers were observed but clinical benefits were not investigated. The most promising study to date was conducted in 12 patients administered 1000 IU/day over 28 weeks, which reduced the number of gadolinium enhancing lesions on the magnetic resonance imaging (MRI) of one subject (Smolders et al 2008).

Lupus (SLE)

There is growing evidence suggesting an aetiological role for vitamin D in SLE, as in MS and other autoimmune diseases. In addition to epidemiological studies showing low 25(OH)D in SLE patients compared to healthy controls, and inverse correlations between vitamin D status and disease severity, individuals with this condition are identified as being at high risk of vitamin D deficiency because of a range of factors (Cutolo & Otsa 2008, Kamen & Aranow 2008). These factors include increased photosensitivity, renal involvement impeding bioactivation and evidence of anti-D antibodies in select patient subsets. Data from animal and in vitro studies also point to vitamin D as an effective treatment, in particular reversing the characteristic immune abnormalities, while experimentally induced deficiencies exacerbate clinical features. Interventional studies in SLE patients are now required to confirm this indication.

Psoriasis

As a regulator of cellular growth and differentiation in various tissues, vitamin D has been investigated in psoriasis. The active form of vitamin D and its analogues have been found to suppress growth and stimulate the terminal differentiation of keratinocytes.

Vaginal atrophy

Animal studies have revealed the presence of VDR in the cells lining the vagina (Yildirim et al 2004a). Given the established role of vitamin D in regulating growth and differentiation of tissues, especially those lining stratified squamous epithelium, a possible role for vitamin D in the prevention and treatment of vaginal atrophy associated with menopause is being considered (Yildirim et al 2004b). A number of studies involving co-administration with

Clinical note — A link between vitamin D and schizophrenia?

The epidemiological correlation between babies born in winter and spring and an increased prevalence of schizophrenia has been a long-established phenomenon and presented many riddles for researchers (Kendell & Adams 2002). The association has also been observed in cities where air pollution reduces UV irradiation, and, more recently, a 7–10-fold increased risk has been identified in second-generation dark-skinned migrants. These observations have led to the emergence of a neurodevelopmental theory of schizophrenia, which suggests that low prenatal vitamin D interferes with brain development by interacting with D-responsive/susceptible genes to create the currently recognised polygenic effects of schizophrenia (Mackay-Sim et al 2004).

A significant progression of this theory was made at the Queensland Centre for Schizophrenic Research led by Professor John McGrath. The centre's work has taken the level of evidence beyond the early epidemiological findings, with research being conducted to assess the impact of vitamin D deficiency on animal brains and in vitro cultures. Research has also been conducted to measure third-trimester serum 25(OH)D levels in schizophrenic and schizoaffective mothers, while investigating the impact of vitamin D supplementation prior to 1 year of age in the infants and the subsequent risk reduction for the disease in later life (McGrath et al 2003, 2004a, 2004b). The preliminary evidence to date shows weak support for this hypothesis, with a consistent positive relationship appearing for males, and evidence pointing towards a stronger relationship in dark-skinned populations compared to fairer skinned populations.

calcium have produced some positive results; however, a recent trial of calcium and D_3 (500 mg/day and 400 IU/day, respectively) used as a replacement for transdermal oestrogen replacement therapy in menopausal women over 1 year revealed an objective worsening of vaginal atrophy (Checa et al 2005). Dose, however, may be an issue.

DOSAGE RANGE

Acceptable daily intake (ADI)

The NHMRC vitamin guidelines released in 2006 make the following recommendations for ADI:

- Children and adults < 50 years: 200 IU/day.
- Adults 51–70 years: 400 IU/day.
- Adults over 70 years: 600 IU/day.

The ADI is based on the amount of vitamin D required to maintain serum 25(OH)D at a level of at least 27.5 nmol/L with minimal sun exposure. The level has been raised in the 51–70 year age group to account for the reduced capacity of the skin to produce vitamin D with ageing. The higher level recommended in the over 70 years group was made because this group tends to have less exposure to sunlight.

According to clinical studies

(D_3 supplemental form unless otherwise indicated.)

- Uncomplicated rickets: 1600 IU/day for the first month, gradually reducing the dose to 400 IU.
- Osteomalacia: 36,000 IU/day with calcium supplementation.
- Rickets and osteomalacia due to defective metabolism: 50,000–300,000 IU/day.
- Pregnancy supplementation: two large doses of 600,000 IU in the seventh and eighth months (Marya et al 1981).
- Reduction in fractures associated with osteoporosis: prevention of fractures has resulted from as little as 200 IU/day in combination with calcium, but the most effective dose is ≥ 800 IU/day in combination with ≥ 1200 mg/day calcium.
- Reduction in falls: 1000 IU/day in combination with 1000 mg/day calcium.
- Hyperparathyroidism: 2.5–6.25 mg/day.
- Hepatic osteodystrophy: 4000 IU/day.
- Anticonvulsant osteomalacia: 4000 IU D_2/day for 105 days, followed by 1000 IU/day.
- Systemic scleroderma: 0.75–1.25 μg D_3 for 6 months.

TOXICITY

Toxic ingestion of prescribed forms of vitamin D or excessive dietary consumption of either D_2 or D_3 has been reported in the vicinity of 50,000–100,000 IU/day or 10,000 IU/day taken routinely for several months. Obtaining such enormous amounts from unfortified foods is improbable. Traditionally the toxicity picture of vitamin D has been attributed to a secondary hypercalcaemia, which manifests as anorexia, nausea, vomiting, polyuria, muscle pain, unusual tiredness, dry mouth, persistent headache and secondary polydipsia. Over extended periods of time, this state of hypervitaminosis can result in metastatic calcification of soft tissues including kidney, blood vessels, heart and lungs. Symptoms and signs at this later stage include cloudy urine, pruritis, drowsiness, weight loss, sensitivity to light, hypertension, arrhythmia, fever and abdominal pain. Toxic levels cannot be obtained from excessive sun exposure (FAO/WHO 2002, Gropper et al 2009). More recent research into vitamin D pharmacokinetics, however, points towards 25(OH)D's ability at high doses to displace $1,25(OH)_2D$ from VDR, therefore increasing free concentrations of the active form and subsequent gene transcription (Jones 2008).

ADVERSE REACTIONS

High doses of supplements may induce the following:

- arterial calcification
- arrhythmia
- gastrointestinal distress, including nausea, vomiting and constipation
- hypercalcaemia
- nephrotoxicity, manifesting as polyuria, polydipsia and nocturia.

SIGNIFICANT INTERACTIONS

Only those interactions relevant to the oral supplemental forms of vitamin D will be reviewed.

A number of pharmacokinetic and pharmacodynamic interactions are possible with vitamin D and a range of medicines and minerals.

Antituberculosis drugs

Drugs such as rifampicin and isoniazid have been reported to induce catabolism of vitamin D and in some cases manifest as reduced levels of metabolites. This may represent a concern in those patients already at risk of poor vitamin D status (Harkness & Bratman 2003).

Calcium-channel blockers

Vitamin D supplementation may reduce effectiveness of these drugs. Use with caution unless under medical supervision (Harkness & Bratman 2003).

Glucocorticoids

In high doses, these drugs directly inhibit vitamin-D-mediated calcium uptake in the gastrointestinal tract and through unknown mechanisms may deplete levels of active vitamin D (Wilson et al 1991). During long-term therapy with either oral or inhaled corticosteroids, calcium and vitamin D supplementation should be considered.

Ketoconazole

This drug reduces the conversion of vitamin D to its active forms. Increased vitamin D intake may be required with long-term drug use.

Lipid-lowering drugs

Drugs such as cholestyramine and colestipol may compromise the absorption of all fat-soluble vitamins. To avoid the interaction, administer the supplement at least 1 hour prior to or 4–6 hours after ingestion of the drug (Harkness & Bratman 2003). Conversely, long-term use of statins is

associated with increased 25(OH)D levels via an unknown mechanism (Aloia et al 2007).

Magnesium
Either an excess or inadequate level of magnesium can impact on vitamin D status. The final hydroxylation step to $1,25(OH)_2D_3$ is dependent upon magnesium and a deficiency would compromise this. However, high levels of magnesium, mimicking calcium, can suppress PTH secretion, also suppressing the activation phase (Groff & Gropper 2005). Therefore magnesium levels within the normal range will enhance activation of vitamin D to its active form.

Mineral oil
Mineral oil impairs absorption of all fat-soluble nutrients and may therefore deplete oral intake of vitamin D sources. Separate doses by at least 2 hours.

Oestrogens
Vitamin D works synergistically with oestrogens to prevent bone loss. Interaction is beneficial.

Orlistat
Although orlistat has been shown to reduce the absorption of some fat-soluble nutrients, its effect on vitamin D specifically remains unclear. Concurrent supplementation of a multivitamin with D is advised. Separate doses by a minimum of 4 hours either side of ingestion of orlistat (Harkness & Bratman 2003).

Phenytoin and valproate
The anticonvulsants induce catabolism of vitamin D through liver induction and prolonged use is associated with increased risk of developing rickets and osteomalacia.

CONTRAINDICATIONS AND PRECAUTIONS
- Hypersensitivity to vitamin D.
- Hypercalcaemia.
- Not to be taken in sarcoidosis or hyperparathyroidism without medical supervision.
- Possible interference with the action of calcium-channel blockers.
- High doses require medical supervision in patients with arteriosclerosis and heart disease.
- High doses capable of inducing hypercalcaemia may precipitate arrhythmias in patients taking digitalis.

PREGNANCY USE
Vitamin D supplements as either D_2 or D_3 are exempt from pregnancy classification by the TGA, which reflects their safety in pregnancy and lactation (Australian Drug Evaluation Committee 1999).

PATIENTS' FAQs
What will this vitamin do for me?
Vitamin D is essential for health and wellbeing. It plays a critical role in regulating calcium and phosphorus levels in the body, and is important for healthy bones and preventing abnormal cell changes, which may increase the risk of some cancers.

PRACTICE POINTS/PATIENT COUNSELLING
- Vitamin D has a critical role in bone growth and development, but also has diverse roles throughout the body, including inhibiting abnormal proliferation of cells.
- Most vitamin D is endogenously produced through sun exposure and an activation process that involves both the liver and the kidneys; food sources represent a secondary and often unreliable source. Those groups in the community who have restricted sun exposure are at the greatest risk of a deficiency, including the elderly, newborns, institutionalised, adolescents and young children with marginal calcium intake during rapid growth periods, and those with dark skins.
- In the prevention of falls and prevention or treatment of osteoporosis, vitamin D supplements are most commonly given in combination with other nutrients, such as calcium.
- Other uses for vitamin D include: supplementation during pregnancy to increase fetal levels; correction of deficiencies that may result from medications or malabsorptive diseases such as coeliac disease, Crohn's disease and cystic fibrosis; as a protective agent against breast, prostate and colorectal cancer; and for a variety of metabolic bone disorders.

When will it start to work?
This will depend on the condition being treated. In uncomplicated rickets, serum levels should begin to rise in 1–2 days, and after 3 weeks signs of calcium and phosphorus mineralisation appear on X-ray.
Are there any safety issues?
Vitamin D is considered a safe supplement when used in the recommended doses; however, it may interact with some medicines.

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Vitamin E

HISTORICAL NOTE Vitamin E was first discovered in 1922 at the University of California in Berkeley when it was observed that rats required the nutrient in order to maintain their fertility. In this way, vitamin E became known as the antisterility vitamin, which is reflected in its name, as *tokos* and *pherein* are the Greek words for 'offspring' and 'to bear'. Although considered an essential nutrient, it was not until the mid-1960s that deficiency states in humans were first identified. More specifically, deficiency was detected in children with fat malabsorption syndromes (Shils 1999, Wahlqvist 2002).

BACKGROUND AND RELEVANT PHARMACOKINETICS

Alpha-tocopherol is absorbed from the intestinal lumen and is dependent upon adequate fat digestion. After micellisation, it enters the lymphatic circulation and then the systemic circulation where it is transported in chylomicrons. Breakdown of chylomicrons in the blood releases some vitamin E, which is then taken up by circulating lipoproteins such as LDL and HDL. The remaining vitamin E is transported via chylomicron remnants to the liver. Here, the RRR alpha-tocopherol form is preferentially secreted back into the circulation in VLDL. It is suspected that hepatic alpha-tocopherol transfer protein is responsible for discriminating between the different types of tocopherols at this point (with the natural form preferentially taken up). Vitamin E is ultimately delivered to tissues when chylomicrons and VLDL are broken down by lipoprotein lipase. Vitamin E transported by LDL is also taken up by tissues via the LDL receptor. The bulk of vitamin E is stored in adipose tissue, although some storage also occurs in the heart, muscles, testes, uterus, adrenal and pituitary glands, and blood. Vitamin E metabolites are mainly excreted in the faeces, although some is also excreted by the kidneys and the skin (Shils 1999).

CHEMICAL COMPONENTS

To date, eight different naturally occurring compounds have been identified and named as alpha-, beta-, gamma- and delta-tocopherol and alpha-, beta-, gamma- and delta-tocotrienol. Acetate and succinate derivatives of natural and synthetic forms of vitamin E also have vitamin E-like activity, although the strength of activity varies between the different compounds and is less than the naturally occurring RRR stereoisomer D-alpha-tocopherol. The human diet generally provides a mixture of compounds with vitamin E activity.

Relative strengths of the various forms of vitamin E

The relative strength of the different forms of vitamin E can be expressed as either alpha-tocopherol equivalents (alpha-TE) or international units (IU). One alpha-TE represents the activity of 1 mg RRR-alpha-tocopherol (D-alpha-tocopherol), and the alpha-TE of natural forms of vitamin E can be calculated using simple mathematics. The number of milligrams of beta-tocopherol should be multiplied by 0.5, gamma-tocopherol by 0.1 and alpha-tocotrienol by 0.3, whereas any of the synthetic all-*rac*-alpha-tocopherols (DL-alpha-tocopherol) should be multiplied by 0.74 (FAO/WHO 2002).

More commonly, activity is described in terms of International Units (IU), where 1 mg of synthetic all-*rac*-alpha-tocopherol (DL-alpha-tocopherol) acetate is equivalent to 1 IU of vitamin E. Relative to this, 1 mg of DL-alpha-tocopherol is equal to 1.1 IU, 1 mg of D-alpha-tocopheryl acid succinate is equal to 1.21 IU and 1 mg of D-alpha-tocopheryl acetate is equal to 1.36 IU. The natural form of D-alpha-tocopherol has the highest biopotency, which is equal to at least 1.49 IU (Meydani & Hayes 2003).

FOOD SOURCES

Vitamin E is found in various forms in both animal and plant foods. The richest food sources of vitamin E are cold-pressed vegetable oils, particularly wheatgerm oil, and nuts and seeds. Other sources include spinach, kale, sweet potatoes, yams, egg yolk, liver, soya beans, asparagus and dairy products such as butter and milk. Frying, processing, bleaching, milling and freezing foods will remove some of

the vitamin E content. Overall, up to 55% can be lost through cooking (Wahlqvist 2002).

DEFICIENCY SIGNS AND SYMPTOMS

Owing to the widespread availability of vitamin E in the food chain, it is generally accepted that primary vitamin E deficiency does not occur. However, deficiency has been reported in low-birth-weight infants given infant formula or cow's milk with low vitamin E levels, and in some intestinal malabsorption syndromes such as cystic fibrosis. Genetic abnormalities in alpha-tocopherol transport protein also result in vitamin E deficiency (Shils 1999).

Ultimately, it is tissue uptake, local oxidative stress levels and polyunsaturated fat content that influence whether symptoms of deficiency develop.

Symptoms of deficiency tend to be vague and difficult to diagnose because of the nutrient's widespread actions, but the following signs and symptoms have been reported in humans (FAO/WHO 2002, Meydani & Hayes 2003):

- haemolytic anaemia
- immunological abnormalities
- neurological disturbances (e.g. peripheral neuropathies)
- platelet dysfunction
- leakage of muscle enzymes such as creatine kinase and pyruvate kinase into plasma
- increased levels of lipid peroxidation products in plasma.

MAIN ACTIONS

Vitamin E is an electron donor (reducing agent or antioxidant), and many of its biochemical and molecular functions can be accounted for by this function. It is involved in many biochemical processes in the body, but its most important biological function is that of an antioxidant and working within the antioxidant network.

Antioxidant

Vitamin E is considered to be the most important and potent lipid-soluble antioxidant. It prevents free-radical damage to the polyunsaturated fatty acids (PUFAs) within the phospholipid layer of each cell membrane and oxidation of LDL. It has been estimated that for every 1000–2000 molecules of phospholipid, one molecule of vitamin E is present for antioxidant defence (Sen & Packer 2000).

This is achieved by reacting with free-radical molecules and forming a tocopheroxyl radical, which then leaves the cell membrane. Upon entering the aqueous environment outside the membrane, it reacts with vitamin C (or other hydrogen donors such as glutathione) to become reduced and, therefore, regenerated (Vatassery 1987). In this way, vitamin E activity is influenced by what has been called the 'antioxidant network', which restores vitamin E to its unoxidised state, ready to act as an antioxidant many times over (see Clinical note for more information).

Taking a larger perspective, the collective antioxidant action at each cell membrane protects the body's tissues and organs from undue oxidative stress. Prolonged and/or excessive exposure to free radicals has been implicated in many conditions, such as cardiovascular disease, cancer initiation and promotion, degenerative diseases, and ageing in general (FAO/WHO 2002).

Regulates immunocompetence

Vitamin E increases humoral antibody production, resistance to bacterial infections, cell-mediated immunity, the T-lymphocyte response, TNF production and NK cell activity, thereby playing a role in immunocompetence. It also decreases PGE_2 production and therefore reduces its immunosuppressive effects and decreases levels of lipid peroxides

Clinical note — Free radicals, antioxidant recycling and the antioxidant network

Oxygen-containing free radicals (such as the hydroxyl radical, superoxide anion radical, hydrogen peroxide, oxygen singlet and nitric oxide radical) are highly reactive species, capable of damaging biologically important molecules such as DNA, proteins, carbohydrates and lipids. Antioxidants can break the destructive cascade of reactions initiated by free radicals by converting them into harmless derivatives.

The term 'oxidative stress' refers to an imbalance of pro-oxidants over antioxidants. The term 'antioxidant capacity' is a measure of the sum of available endogenous and exogenous defence mechanisms that work synergistically to restore and maintain the oxidative balance. During the process of maintaining oxidative balance, antioxidants such as vitamin E become oxidised themselves. Other antioxidants, such as ubiquinone, ascorbate and glutathione, are then involved in recycling vitamin E back to its unoxidised state, allowing it to continue neutralising free-radical molecules (Sen & Packer 2000). When these other antioxidants become oxidised in turn, they are also regenerated to their antioxidant forms by yet others, such as alpha-lipoic acid and cysteine. In this way, the recycling of various antioxidants occurs in an orchestrated manner. The interactions between antioxidant substances have been described as the 'antioxidant network', which comprises four parts that work together to provide a continuous defence against free-radical damage (De Vita et al 2006). These are:

- enzymes that destroy or detoxify common oxidants (e.g. catalase, glutathione peroxidase, which needs selenium)
- antioxidant vitamins, notably vitamins E and C, and coenzyme Q10, which are continuously recycled, as discussed earlier
- dietary antioxidants or phytochemicals (e.g. carotenoids, polyphenols and allyl sulfides).
- proteins that sequester iron and copper so that free forms do not exist in the body.

The antioxidant network provides a basis for recommending combinations of foods and antioxidant nutrients to provide maximal benefits, rather than single entities in high doses.

that can also adversely affect immune function (Meydani 1995).

OTHER ACTIONS

- Regulates vascular smooth-muscle-cell proliferation.
- Inhibits smooth-muscle-cell proliferation by inhibiting protein kinase C activity.
- Inhibits phospholipase A2 activity, suppressing arachidonic acid metabolism.
- Antiplatelet activity has been demonstrated in vitro, but in vivo tests have been inconsistent for D-alpha-tocopherol.
- Modulates vascular function by regulating the enzymatic activities of endothelial nitric oxide synthase (eNOS) and NAD(P)H oxidase (Ulker et al 2003).
- Analgesic activity: most likely mediated via inhibitory effects on COX-2 and 5-lipooxygenase.
- Promotes wound healing.
- Exerts neuroprotective effects.
- Gene regulation. Vitamin E modulates genes involved in cholesterol homeostasis, atherosclerosis, inflammatory pathways and cellular trafficking, including of synaptic vesicular transport and the synthesis pathways of neurotransmitters (Munteanu et al 2004, Brigelius-Flohe 2009).
  - More specifically, vitamin E regulates genes encoding proteins involved in apoptosis (CD95L, Bcl2-L1), cell-cycle regulation (p27, cyclin D1, cyclin E), cell adhesion (E-selectin, L-selectin, ICAM-1, VCAM-1, integrins), cell growth (CTGF), extracellular matrix formation/degradation (collagen alpha-1(1), glycoprotein IIb, MMP-1, MMP-19), inflammation (IL-1-beta, IL-2, IL-4, TGF-beta), lipoprotein receptors (CD36, SR-BI, SR-AI/II, LDL receptor), transcriptional control (PPAR-gamma), metabolism (CYP3A4, HMG-CoA reductase, gamma-glutamylcysteine synthetase), and other processes (leptin, a beta-secretase in neurons, tropomyosin), activation of the cellular retinoic acid-binding protein II (CRABP-II) (Brigelius-Flohe 2009).

CLINICAL USE

Although vitamin E supplementation is used to correct or prevent deficiency states, most uses are based on the concept of high-dose supplements acting as therapeutic agents to either prevent or treat various health conditions.

Deficiency: prevention and treatment

Traditionally, vitamin E supplementation has been used to treat deficiency or prevent deficiency in conditions such as genetic abnormalities with alpha-tocopherol transfer protein, apolipoprotein B, or microsomal triglyceride transfer protein (Shils 1999); and to treat fat malabsorption syndromes (e.g. chronic cholestasis, cystic fibrosis, short bowel syndromes such as Crohn's disease, chronic steatorrhea, coeliac disease, chronic pancreatitis and TPN).

Cardiovascular disease

Oxidative stress has been shown to play an integral role in the formation, progression and rupture of the atherosclerotic plaque via modification of proteins and DNA, alteration in gene expression, promotion of inflammation and endothelial dysfunction, enhancement of surface adhesion molecules expression, LDL oxidation, metalloproteinase (MMP) production and consequently plaque rupture (Katsiki & Manes 2009). Based on these observations and evidence largely from epidemiological studies, investigation of various antioxidant substances, in particular vitamin E, has been conducted to determine their role in primary and/or secondary prevention of cardiovascular disease.

Vitamin E is best known for its effects on the cardiovascular system, as it inhibits platelet aggregation and adhesion, and smooth-muscle-cell proliferation, has an anti-inflammatory effect on monocytes, improves endothelial function and decreases lipid peroxidation (Kaul et al 2001). It also modulates the expression of genes that are involved in atherosclerosis (e.g. scavenger receptors, integrins, selectins, cytokines, cyclins) (Munteanu et al 2004). Its ability to reduce oxidative stress, both directly and indirectly as part of the antioxidant network, is of particular importance because oxidation of LDL is a key process in atherogenesis, enhancing foam-cell and early lesion formation (Terentis et al 2002).

Epidemiological and clinical studies

In 1946 Canadian physicians first reported that vitamin E could protect against coronary heart disease; however, it was not until the results of two very large human studies were published nearly 50 years later that the greater scientific community and the public started to take note of vitamin E. In 1993, the prospective Nurses' Health Study and the Health Professionals' Follow-up study both reported that, compared to non-users, vitamin E supplementation at a dose of at least 100 IU for at least 2 years significantly reduced the risk of coronary disease by an estimated 40% (Rimm et al 1993, Stampfer et al 1993).

The prospective Nurses' Health Study followed 87,245 women aged 34–59 years without known coronary disease over 8 years and found that those women with the highest intake of vitamin E had the lowest relative risk of non-fatal myocardial infarction (MI) or death from coronary disease, compared to those with the lowest intake (Stampfer et al 1993). Interestingly, short-term use or dietary intake alone did not produce the same significant reduction. The Health Professionals' Follow-up study observed 39,910 men aged 40–75 years over 4 years and produced similar results, finding that long-term vitamin E (at least 100 IU/day) significantly reduced the relative risk of coronary disease compared to non-users (Rimm et al 1993).

Subsequently, a double-blind study conducted at Cambridge University, UK, and published in 1996 supported these results, but further suggested that higher doses could produce benefits more quickly and more dramatically (Stephens et al 1996). The placebo-controlled randomised study known as the Cambridge Heart Antioxidant Study (CHAOS) involved 2002 patients with angiographically proven coronary atherosclerosis, and compared the effects of two different strengths of alpha-tocopherol supplementation (400 IU and 800 IU)

and a placebo over a median of 510 days. Treatment with either dose of vitamin E was seen to reduce the risk of cardiovascular death and non-fatal MI by over 75%, with effects established after 12 months.

In 1999, results from the large GISSI trial were published, which were conflicting results (Albert et al 1999, GISSI 1999). The trial, which involved 11,324 patients who had recently survived a MI (< 3 months), investigated the effects of three different treatment protocols compared to a placebo: 1 g omega-3 fatty acid/day, 300 IU synthetic vitamin E/day, fish oils plus vitamin E/day, or a placebo. The four groups were observed for nearly 4 years for cardiovascular disease morbidity and mortality. Results showed that the fish-oil treatment groups had significantly decreased combined end-points of death, non-fatal MI and stroke over this time, whereas the vitamin E treatment produced little effect. The trial has since been criticised because the form of vitamin E used was synthetic and the dose was relatively low compared to doses in other studies involving patients with preexisting disease.

To date, 18 different randomised studies in the peer-reviewed literature have evaluated vitamin E in people at risk of CVD or with clinically diagnosed CVD (Katsiki & Manes 2009). The larger studies — GISSI (GISSI 1999), Women's Antioxidant Cardiovascular Study (WACS) and Alpha-Tocopherol Beta-Carotene (ATBC) Cancer Prevention study — have resulted in several published papers as researchers analyse effects in sub-groups or results are re-evaluated using different models. Overall, 8 randomised studies have tested vitamin E as a sole treatment, four studies have studied vitamin E in combination with vitamin C supplementation, and six have used multiple vitamin combinations which included vitamin E. The dose of vitamin E administered varies considerably from 55 IU to 800 IU daily and in at least five studies, synthetic vitamin E was used. In general, studies using natural

Clinical note — Confusing results for vitamin E

To date, many in vitro, animal and epidemiological studies support the use of vitamin E in the prevention of cardiovascular disease (Clarke & Armitage 2002). However, intervention studies are equivocal. Many factors could account for the lack of benefit on the primary end-point in the majority of trials.

1. Dose selection

A closer look at the evidence shows that dose selection varies enormously from levels just above the RDI (50 mg/day) to large doses of 800 IU/day. Clinical research reveals that a daily dose of at least 400 IU is required for LDL to become less susceptible to oxidation (Brockes et al 2003) and an effective threshold dose may be as high as 800 IU/day (Jialal & Devaraj 2005a).

2. Biomarkers of oxidative stress

Just as the statin trials investigate subjects with high cholesterol levels rather than the general population, it can reasonably be assumed that antioxidant treatment is best suited to those people with increased oxidative stress rather than the general population, yet researchers consistently fail to consider this as a biochemical basis for patient inclusion (Meagher 2003). The levels of oxidised amino acids in urine and plasma can reflect those in tissues and identify people with high levels of oxidative stress; this may be one method of subject selection (Heinecke 2002).

3. Type of supplement

In the specific case of vitamin E, the form of tocopherol used is crucial, as synthetic forms have less biological activity than RRR D-alpha-tocopherol. According to a 2002 FAO/WHO report, cross-country correlations between coronary heart disease mortality in men and the supply of vitamin E homologues acrsoss 24 European countries shows a highly significant ($P < 0.001$) correlation for D-alpha-tocopherol, whereas all other forms of vitamin E do not achieve statistical significance.

In the last few years, it has further been proposed that the lack of efficacy of commercial tocopherol preparations in some clinical trials may be due to the absence of other natural tocopherols, primarily gamma- and delta-tocopherol. Preliminary studies provide some support for this view (Jialal & Devaraj 2005a, Saldeen & Saldeen 2005). Studies using different mixtures of alpha-, beta-, gamma- and delta-tocopherol have found that a mixture of gamma-, delta- and alpha-tocopherol with the ratio of 5:2:1 have a much better antioxidant effect than alpha-tocopherol alone. This mixture is similar to that found in nature. In human and animal studies, the mixed tocopherol preparation also had much more favourable effects on constitutive NO synthase (ecNOS) and superoxide dismutase activity than alpha-tocopherol, and in a rat model was more effective in decreasing platelet aggregation and inhibiting thrombus formation. A mixed tocopherol preparation is also superior to alpha-tocopherol in terms of myocyte protection (Chen et al 2002).

4. Plasma vitamin E levels

The measurement of plasma vitamin E levels in the supplemented groups has been inconsistent in the studies, so it is uncertain whether levels significantly rose in response to treatment and subjects were compliant. For example, in the CHAOS, ASAP, ASAP follow-up and SPACE studies, a significant increase in the plasma antioxidant levels was reported and all studies found a benefit on the primary end-point, whereas measurement of plasma levels has been inconsistent in the negative studies (Jialal & Devaraj 2005a).

Clearly, the optimal form/s, dosage regimen, duration of use and subpopulation best suited to primary and secondary preventative treatment still need to be clarified with future trials.

TABLE 1 Summary of Positive Findings from Randomised Studies of Vitamin E in Primary or Secondary CVD Prevention

Name of study	Prevention goal	Number of subjects	Characteristics	Daily intervention	Findings
CHAOS (Stephens et al 1996)	Secondary	2002	Coronary disease	Natural vitamin E (400 IU or 800 IU)	Vitamin E reduced risk of cardiovascular death and non-fatal MI by over 75%.
SPACE (Boaz et al 2000)	Secondary	2198	End-stage renal disease – people on haemodialysis with preexisting CV event	Natural vitamin E (800 IU)	Vitamin E caused a 50% reduction in cardiac events.
CLAS (Azen et al 1996)	Secondary	146	Non-smoking 40–59-year-old men with previous coronary artery bypass graft surgery	Vitamin E (< or > 100 IU) and vitamin C (< or > 250 mg)	Higher vitamin E intake was associated with less carotid IMT progression compared with low vitamin E users in people not treated with colestipol.
ASAP (Salonen et al 2003)	Primary	520	Smoking/non-smoking men and postmenopausal women aged 45–69 years with elevated serum cholesterol	Twice daily either (136 IU) of D-alpha-tocopherol, 250 mg of slow-release vitamin C, a combination of these, or a placebo, for 3 years	The proportion of men with progression of carotid atherosclerosis was reduced by 74% with combination of vitamins E and C compared to the placebo; no significant effect was seen in women.
ASAP follow-up (Salonen et al 2003)	Primary	520	Smoking/non-smoking men and postmenopausal women aged 45–69 years with elevated serum cholesterol	Twice daily (136 IU) of D-alpha-tocopherol, 250 mg of slow-release vitamin C, or a placebo, for 6 years	Effect was still significant after a further 3 years: combined vitamins E and C continued to slow down atherosclerotic progression in hypercholesterolaemic men.
ATBC (Rapola et al 1996)	Primary: incidence of angina pectoris	29,134	Finnish male smokers aged 50–69 years with no history of MI	Synthetic vitamin E (55 IU), beta-carotene (20 mg), or both, or a placebo	Vitamin E was associated with a minor decrease in incidence of angina pectoris.
ATBC (Virtamo et al 1998)	Primary and secondary	29,134	Finnish male smokers aged 50–69 years with no history of MI	Synthetic vitamin E (55 IU), beta-carotene (20 mg), or both, or a placebo	Vitamin E decreased incidence of primary major coronary events by 4%; no effect on incidence of non-fatal MI; vitamin E decreased incidence of fatal coronary heart disease by 8%.

TABLE 1 Summary of Positive Findings from Randomised Studies of Vitamin E in Primary or Secondary CVD Prevention (*continued*)

Name of study	Prevention goal	Number of subjects	Characteristics	Daily intervention	Findings
ATBC (subset) (Leppala et al 2000)	Primary: prevention of incident and fatal subarachnoid, intracerebral haemorrhage, cerebral infarction and stroke	29,134	Finnish male smokers aged 50–69 years with no history of MI	Synthetic vitamin E (55 IU), beta-carotene (20 mg), or both, or a placebo	Vitamin E prevented ischaemic stroke in high-risk hypertensive patients.
WACS (Cook et al 2007)	Secondary	8171	Women with CVD or at least 3 risk factors	Vitamin C (500 mg/day), natural vitamin E (600 IU every other day), and beta-carotene (50 mg every other day)	Vitamin E significantly reduced incidence of stroke and produced a marginally significant reduction in the primary outcome (a combination of MI, stroke, coronary revascularisation, or CVD death) in a prespecified subgroup of women with prior CVD.
IEISS (Singh et al 1996)	Secondary	125	Patients with suspected acute MI	Vitamin E (400 mg), vitamin A (50,000 IU), vitamin C (1000 mg), beta-carotene (25 mg)	Treatment reduced mean infarct size, angina pectoris and total arrhythmias; poor left ventricular function occurred less often with antioxidants; cardiac end points were significantly less in the antioxidant group (20.6% vs 30.6%, respectively).
Fang et al 2002	Secondary	40	After cardiac transplantation	Twice daily vitamin C (500 mg) plus vitamin E (400 IU)	Supplementation with vitamins C and E retarded early progression of transplant-associated coronary arteriosclerosis compared to the placebo.

TABLE 2 Summary of Negative Findings from Randomised Studies of Vitamin E in Primary or Secondary CVD Prevention

Name of study	Prevention goal	Number of subjects	Characteristics	Daily intervention	Results
GISSI (Albert et al 1999)	Secondary	11,324	Post-MI	Synthetic vitamin E (300 mg/day), fish oils (1 g/day), combination of fish oil and vitamin E, or a placebo	There was no significant reduction in the combined end-points of death, non-fatal MI and stroke.
GISSI (Marchioli et al 2006)	Secondary	8415	Post-MI patients without CHF at baseline	Synthetic vitamin E (300 mg/day), fish oils (1 g/day), combination of fish oil and vitamin E, or a placebo	Vitamin E treatment was associated with a significant 50% increase of CHF in patients with left ventricular dysfunction (ejection fraction < 50%).
HOPE (Yusuf et al 2000)	Primary and secondary	9541	2545 women and 6996 men 55 years of age or older who were at high risk of cardiovascular events because they had cardiovascular disease or diabetes in addition to one other risk factor	Natural vitamin E (400 IU), and a placebo or angiotensin-converting-enzyme inhibitor (ramipril), or both	There was no significant effect on the primary outcome, which was a composite of MI, stroke and death from cardiovascular causes.
MICRO-HOPE (Lonn et al 2005)	Secondary	3654	Middle-aged and elderly people with diabetes and CV disease and/or additional coronary risk factor(s)	Vitamin E (400 IU) for an average of 4.5 years	Vitamin E had no effect on CV outcomes or nephropathy.
PPP (de Gaetano 2001)	Primary	4495	Those at risk of CVD: people with hypertension, hypercholesterolaemia, diabetes, obesity, family history of premature MI, or the elderly	Vitamin E (300 mg)	There was no significant reduction in CV events.
VEAPS (Hodis et al 2002)	Primary	353	Elevated LDL-C	Vitamin E (400 IU)	Significantly reduced circulating oxidized LDL and LDL oxidative susceptibility. Vitamin E supplementation did not reduce the progression of carotid artery far-wall intima-media thickness over a 3-year period.
ATBC (subset) (Rapola et al 1997)	Secondary	1862	Finnish male smokers with previous MI	Synthetic vitamin E (55 IU), beta-carotene (20 mg), or both, or a placebo	Risk of fatal coronary heart disease increased in groups receiving either beta-carotene or vitamin E and beta-carotene. There was a non-significant trend of increased deaths in the vitamin E group.

TABLE 2 Summary of Negative Findings from Randomised Studies of Vitamin E in Primary or Secondary CVD Prevention (*continued*)					
Name of study	**Prevention goal**	**Number of subjects**	**Characteristics**	**Daily intervention**	**Results**
HPS (Parkinson Study Group 2002)	Secondary	20,536	High CVD risk: coronary disease, other occlusive arterial disease, or diabetes	Vitamin E (600 mg), vitamin C (250 mg), beta-carotene (20 mg)	There were no significant differences in all-cause mortality, or in deaths due to vascular or non-vascular causes; no significant reduction in incidence of non-fatal MI, coronary death, non-fatal or fatal stroke or coronary or non-coronary revascularisation.
MVP (Tardif et al 1997)	Secondary: aimed to decrease incidence and severity of restenosis after angioplasty	317	Before and after coronary angioplasty	One month before angioplasty and for 6 months afterwards: multivitamins (30,000 IU beta carotene, 500 mg vitamin C, and 700 IU vitamin E) twice daily and/or probucol, or a placebo 12 hours before angioplasty given an extra 1000 mg probucol, 2000 IU vitamin E, or both, or a placebo	Multivitamin ineffective at reducing the rate of restenosis.
SUVIMAX (Zureik et al 2004)	Primary	1162	Healthy population	Vitamin C (120 mg), vitamin E (30 mg), beta-carotene (6 mg), selenium (100 micrograms), and zinc (20 mg)	There was no beneficial effect on carotid atherosclerosis and arterial stiffness.

vitamin E tend to produce positive results, showing a benefit on cardiovascular outcomes. Additionally, randomised trials conducted in people with established CVD were also more likely to report a cardioprotective effect than primary prevention studies (Katsiki & Manes 2009).

Restenosis

Restenosis is a major limitation to the long-term success of angioplasty. Therefore, measures that prevent or delay this occurrence are being investigated to extend the beneficial effects of the procedure.

Studies in experimental models have shown that vitamin E helps to stabilise atherosclerotic plaque after angioplasty and favours vascular remodelling, thereby suggesting that it may be of benefit in preventing or slowing restenosis (Orbe et al 2003). An early double-blind study using oral synthetic vitamin E (1200 IU) for 4 months found that treatment did not significantly reduce the rate of restenosis after percutanous transluminal coronary angioplasty; however, a minor reduction was detected (DeMaio et al 1992).

The MVP trial by Tardif et al, which aimed to decrease the incidence and severity of restenosis after angioplasty, involved 317 patients due for coronary angioplasty who were given a combination of vitamins, including vitamin E (Tardif et al 1997). One month before surgery and for 6 months afterwards, patients were administered multivitamins (30,000 IU beta carotene, 500 mg vitamin C, and 700 IU vitamin E) twice daily and/or probucol, or a placebo. Twelve hours before angioplasty, they were given an extra 1000 mg probucol, 2000 IU vitamin E or both, or placebo. Treatment with probucol was effective, whereas the multivitamin treatment did not significantly reduce the rate of restenosis.

Angina pectoris

Low-dose vitamin E supplements (50 mg/day) produce a minor decrease in the incidence of angina pectoris in smokers without previous coronary heart disease, according to a RCT (Rapola et al 1996). A smaller study of 29 subjects with variant angina identified six patients who did not respond to calcium-channel blockers and had lower plasma levels than normal but who responded positively to supplementation with 300 mg/day vitamin E. Treatment resulted in a significantly reduced incidence of angina episodes (Miwa et al 1996). Several years later, the same research group identified a transcardiac reduction in plasma vitamin E concentrations concomitant with lipid peroxide formation, suggesting that oxidative stress and vitamin E depletion may be involved in the pathogenesis of coronary artery spasm (Miwa et al 1999).

Nitrate tolerance

Vitamin E supplements (200 mg three times daily) prevented nitrate tolerance when given concurrently with transdermal nitroglycerin (NTG 10 mg/24 hours), according to one randomised, placebo-controlled study in which 24 patients with ischaemic heart disease were compared with 24 healthy volunteers over a 6-day period (Watanabe et al 1997). New research indicates that continuous NTG infusion causes vitamin E depletion, as well as nitrate tolerance, and as the vitamin E levels continue to fall, NTG tolerance becomes greater (Minamiyama et al 2006).

Hypertension

Vitamin E supplementation may reduce blood pressure, LDL oxidation and improve endothelial dysfunction in hypertension, according to current research.

An early double-blind, placebo-controlled study found that DL-alpha-tocopherol nicotinate (3000 mg) significantly reduced SBP from 151.0 to 139.2 mmHg within 4–6 weeks in hypertensive subjects; however, DBP remain unchanged (Iino et al 1977). More recently, long-term vitamin E (200 IU/day) was shown to decrease SBP by 24% in mildly hypertensive patients compared with a 1.6% reduction with a placebo, according to a triple-blind placebo-controlled study conducted over 27 weeks (Boshtam et al 2002). The study involved 70 hypertensive patients (SBP 140–160 mmHg; DBP 90–100 mmHg) aged 20–60 years without other cardiovascular risk factors. Besides reducing SBP, DBP was reduced by 12.5% compared with 6.2% with a placebo.

Some studies have revealed that hypertensive patients have a higher susceptibility to LDL oxidation than normotensive subjects and, therefore, increased atherogenic potential. One study measured the effect of vitamin E (400 IU/day) on the resistance of LDL to oxidation in 47 volunteers (Brockes et al 2003). Comparisons made before and after 2 months' supplementation showed that vitamin E caused a significant increase in the lag time in normotensive and hypertensive patients, ultimately bringing hypertensive patients up to the same point as the healthy controls.

All-cause mortality (ACM)

There is substantial research indicating benefits for vitamin E supplementation in the treatment and prevention of various diseases, but regardless of these benefits, two meta-analyses have drawn the conclusion that vitamin E supplementation increases ACM (Miller et al 2005, Bjelakovic et al 2007). These findings have been unexpected and widely criticised, as they are based on results of smaller studies of variable quality, often involving people with chronic disease and sometimes testing vitamin E as part of a multinutritional intervention and not as a stand-alone treatment. Based on recent re-analysis of the data by Berry et al (2009) and Gerss and Kopcke (2009), which are discussed below, the evidence is not convincing that vitamin E supplementation increases mortality.

In 2005, Miller et al (2005) published a meta-analysis of the dose–response relationship between vitamin E supplementation and total mortality using data from 19 RCTs consisting of a large study population (n = 135,967). A dose–response analysis showed a statistically significant relationship between vitamin E dosage and all-cause mortality. The authors suggested caution with doses of

Clinical note — LDL oxidation and vitamin E
Oxidative stress affects lipid metabolism by producing an oxidised LDL that has greater atherogenic potential than its original form. In the past, attention focused on investigating various antioxidants, such as vitamin E, for their ability to prevent LDL oxidation. In recent years, researchers have started to focus on identifying the biological oxidants responsible for initiating oxidation of LDL within the human arterial wall and on a better understanding of what makes oxidised LDL pro-atherogenic. In 2003, in vitro testing with LDL discovered that myeloperoxidase is a pathway that promotes LDL oxidation in the human artery wall, although others are also likely to exist. It is noteworthy that vitamin E failed to inhibit LDL oxidation by myeloperoxidase in vitro (Heinecke 2003), although it does reduce LDL oxidation in animals and humans when given in doses well above RDI (Brockes et al 2003). If further testing confirms these results, it may mean that vitamin E reduces LDL oxidation in vivo, mainly through its role in the antioxidant network. In other words, its ability to regenerate antioxidants such as vitamin C, coenzyme Q10 and selenium may be more important than its direct antioxidant action.

400 IU/day or higher, while acknowledging that the high-dose studies (≥ 400 IU/day) analysed in the report were often small and performed in patients with chronic diseases.

This meta-analysis has several serious flaws and has been criticised on a number of accounts, inspiring over 40 letters to the journal's editor and hundreds of emails and telephone calls to the authors (Jialal & Devaraj 2005b). In summary, these responses centre on six major flaws. First, results from 12 clinical studies that reported fewer than 10 deaths each were excluded from the meta-analysis, which created the appearance of bias and would have given an artificial weight to studies in which more people died. Second, the meta-analysis included trials of different designs, treatment times, doses, combinations and end-points. Pooling information together from such heterogeneous studies was considered inappropriate. Third, subjects in many studies had significant chronic diseases, such as Parkinson's disease, end-stage renal disease, coronary artery disease, diabetes mellitus and Alzheimer's dementia, which would have influenced their mortality risk. This also means that the results do not necessarily apply to healthy adults taking these supplements. Next, studies used different forms of vitamin E (natural and synthetic) and sometimes used vitamin E in combination with other nutrients; however, results of all these studies were pooled and not separated. Furthermore, subject adherence to the treatment protocol was considered in only one study (CHAOS). Lastly, the use of some statistical models has been questioned.

In 2007, Bjelakovic et al conducted a meta-analysis using data from 68 randomised trials involving 232,606 adults that compared beta carotene, vitamin A, vitamin C (ascorbic acid), vitamin E and selenium, either singly or combined, to a placebo or to no intervention (Bjelakovic et al 2007). When all trials of antioxidant supplements were pooled, there was no significant effect on mortality for vitamin E given singly in high (≥ 1000 IU) or low dose (< 1000 IU). After exclusion of high-bias risk (studies with heterogeneity) and selenium trials, vitamin E given singly or combined with other antioxidants significantly increased mortality, with an estimate of increased mortality of about 5%. A closer look at the details of the study reveals that, of the 815 trials originally identified, 405 trials were excluded from the meta-analysis because mortality was zero (n = 40 000). Vitamin E was administered in doses ranging from 10 to 5000 IU daily, and populations studied were either healthy (primary prevention trials) or had a variety of established diseases such as cancer, CVD, renal disease, hepatitis, systemic lupus erythematosus, heart failure, cirrhosis, gastritis, MI or macular degeneration.

Gerss and Kopcke (2009) recently re-analysed the available data to double-check the findings and concluded that the use of different methodological approaches to meta-analysis will yield contradictory results, with some statistical models finding an association and others not. They used the same data as that described in the Miller et al (2005) meta-analysis and augmented it with an additional 10 trials (2495 additional participants receiving vitamin E doses from 136 to 5000 IU/day). Moreover in two of the originally included trials, updated results of mortality at longer periods of follow-up were available.

More specifically, hierarchical logistic regression analyses confirmed the former results, showing an increased mortality of patients receiving high-dose vitamin E, whereas application of a traditional methodological approach to meta-regression found that in certain trials increased mortality was not due to high-dose vitamin E but could be explained by a higher proportion of male subjects compared to other trials (Gerss & Kopcke 2009). Overall, the causal relationship of vitamin E supplementation and increased ACM is questionable and, in particular, high-dose vitamin E supplementation cannot be regarded as 'proved' to increase mortality.

Similar findings were obtained by Berry et al (2009), who applied a Bayesian meta-analytic method to synthesise results from previous clinical trials of vitamin E. They used data from studies in the Miller et al (2005) meta-analysis, appended by 10 more recent studies and concluded that vitamin E intake is unlikely to affect ACM, regardless of dose.

Re-evaluation of data from the original Framingham Heart Study has also failed to find an association between vitamin E supplementation and increased risk of ACM (Dietrich et al 2009). The Framingham Heart Study (n = 4270) began enrolling in 1948 to investigate the association between supplemental vitamin E and the 10-year incidence of CVD and ACM. Eleven percent of people participating in the study used vitamin E supplements at baseline and the most commonly consumed dose was 300–500 IU/day. In all statistical models, age, diabetes and treatment for blood pressure were significant positive

predictors of CVD and ACM, whereas no statistically significant associations were found between vitamin E supplement intake and CVD and ACM. In secondary analyses, the associations of vitamin E dose and duration of use with CVD and ACM were assessed. Once again, no statistically significant associations were observed in any of the analyses for CVD or ACM. The effect of potential confounders, such as use of aspirin, anti-cholesterol treatment and multivitamins, were minimised using multivariate models which did not change the results.

Parkinson's disease (PD)

Based on experimental and clinical data, it is well established that oxidative stress and lipid peroxidation is increased in the substantia nigra of people with PD and this may play an important role in the disease's aetiology. Vitamin E has therefore been the focus of research as a potential treatment. Using both in vitro and in vivo experimental model systems for PD, studies have demonstrated both vitamin-E-mediated protection and lack of protection (Fariss & Zhang 2003). Similarly, inconsistent results have been obtained for vitamin E supplementation in the prevention and treatment of clinical PD. An open study using high doses of both tocopherol (3200 IU/day) and ascorbic acid (3000 mg/day) delayed the use of levodopa or dopamine agonists for 2 years in subjects with early PD (Fahn 1992). In contrast, the Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism (DATATOP) study found no effect on the progression of disability with a dose of alpha-tocopherol 2000 IU/day (Parkinson Study Group 1996). The same study found vitamin E had no effect on mortality (Parkinson Study Group 1998).

Clinical note — Neurodegenerative disease and oxidative stress

Neurodegenerative diseases are defined by the progressive loss of specific neuronal cell populations and are associated with protein aggregates. A growing body of evidence suggests that oxidative stress plays a key role in the pathophysiology of neurodegenerative disorders such as Alzheimer's dementia and Parkinson's disease. Reactive oxygen species (ROS) are known to cause cell damage by way of three main mechanisms: lipid peroxidation, protein oxidation and DNA oxidation. Cells have developed several defence and repair mechanisms to deal with oxidative stress, and antioxidants such as vitamin E represent the first line of defence. In addition to its antioxidant properties, vitamin E can act as an anti-inflammatory agent, which may also be neuroprotective, and it regulates specific enzymes, thus changing the properties of membranes. The CNS is especially vulnerable to free-radical damage because compared to other tissues it has a high oxygen consumption rate, abundant lipid content and a relative deficit in antioxidant systems. While it remains unclear whether oxidative stress is the primary initiating event associated with neurodegeneration or a secondary effect related to other pathological pathways, a growing body of evidence implicates it as being involved in the propagation of cellular injury (Ricciarelli et al 2007).

Alzheimer's dementia and cognitive decline

The current standard of care for pharmacological management of the cognitive and functional disabilities of Alzheimer's dementia (AD) consists of a cholinesterase inhibitor and sometimes the addition of high-dose vitamin E (Bonner & Peskind 2002). The inclusion of vitamin E is largely based on a 1997 double-blind study that compared a large dose of synthetic vitamin E (1000 IU twice daily) with selegiline (5 mg twice daily) and placebo in a group of patients with moderately severe AD. The 2-year study found that vitamin E significantly slowed down the progression of the disease, delayed institutionalisation and increased survival rate (Sano et al 1997).

Since the 1997 study, numerous dietary and intervention studies have sought to clarify whether vitamin E is protective against the development of various forms of dementia or can slow its progression.

Prevention

Higher plasma vitamin E levels are associated with a significantly reduced risk of cognitive impairment and dementia in older adults. Protection is most consistently seen with vitamin E from food sources, but not always from vitamin E supplements (Cherubini et al 2005, Engelhart et al 2002, Morris et al 2005). According to one study, for every 5 mg/day increase in vitamin E intake, a significant 26% reduction in risk is possible (Morris et al 2005). It now appears that alpha-tocopherol is not the only form of vitamin E exhibiting protective effects. A comparison between the four different tocopherols found naturally in food identified that gamma-tocopherol is also beneficial.

Intervention studies using supplements have produced mixed results and focus on alpha-tocopherol only. The Cache County Study was a large study of 4740 people aged 65 years or older that found a combination of vitamins E (400 IU/day) and C (500 mg/day) taken for at least 3 years was associated with a reduced incidence of AD (Zandi et al 2004). No protective effects were seen when vitamin E or C was taken alone. In the Honolulu/Asia Aging Study, long-term use of vitamin E and C supplements was associated with an 88% reduction in the frequency of subsequent vascular dementia and appeared to improve cognitive function in later life; however, a protective effect against AD was not observed (Masaki et al 2000). A lack of association between dietary or supplemental vitamin E and risk of AD in elderly subjects was also found in the Washington Heights/Inwood Columbia Aging Project (WHICAP), which involved 980 older subjects (Luchsinger et al 2003). It must be noted that dietary intakes were assessed in this study with a limited food frequency questionnaire, which is likely to be less accurate than the more detailed surveys used in some other studies.

Slowing progression

In contrast to the positive 1997 study, a more recent study involving 769 subjects with possible or probable AD using the same dose found no significant effects in patients with mild cognitive impairment and no change to the rate of progression to AD over a 3-year period (Petersen et al 2005).

A Cochrane Systematic Review published in 2008 concluded that there is no evidence of efficacy for vitamin E in the treatment of AD or progression of mild cognitive impairment to AD. However, they used data from only two randomised studies, so further research is required to clarify the issue (Isaac et al 2008).

Immunity in the elderly

Immune cell function is influenced by the oxidant and antioxidant balance, so antioxidant supplements have been investigated clinically for their ability to enhance immune responses (Meydani et al 1998). Increased markers of T-cell-mediated immunity were enhanced with all doses of synthetic vitamin E tested, according to a randomised, double-blind study of 78 healthy elderly subjects. Doses used were 60, 200 and 800 mg/day for 4 months, with best overall responses obtained with the 200 mg dosage (Meydani et al 1997). Another double-blind study found no significant changes to either cellular or humoral immune responses with a low dose of 100 mg/day of synthetic vitamin E taken over 3 months (de Waart et al 1997).

Common cold

Low-dose vitamin E supplementation (50 mg/day) was found to reduce the incidence of the common cold by 28% in a subgroup of men enrolled in the ATBC Cancer Prevention study (Hemila et al 2006). Participants were older city-dwelling men (≥ 65 years) who smoked only 5–14 cigarettes/day. More recently, researchers re-evaluated the data and found that the effect of vitamin E diverged, depending on location of dwelling and smoking status. Among city-dwelling men considered to be low–moderate level smokers (5–14 cigarettes/day), vitamin E significantly reduced common-cold risk, whereas among those smoking more and living away from cities, vitamin E increased common-cold risk. It appears that different modifying factors have an influence on whether vitamin E supplementation has beneficial or harmful effects.

Haemodialysis (HD)

Vitamin E supplementation may offer several benefits to patients on HD, who typically experience high levels of oxidative stress, as there is some evidence that supplementation reduces oxidative stress and LDL oxidability in this population (Badiou et al 2003, Diepeveen et al 2005, Galli et al 2001, Giray et al 2003). The SPACE study by Boaz et al (2000) found that high-dose vitamin E supplementation (natural vitamin E 800 IU/day) caused a 50% reduction in cardiac events. This is a highly significant outcome and worthy of further investigation.

HD patients also experience cramps, which appeared to respond to vitamin E supplementation according to a placebo-controlled, double-blind study of 60 subjects (Khajehdehi et al 2001). Treatment with a vitamin E dose of 400 mg/day for 8 weeks resulted in a 54% reduction in cramps, which increased to a 97% reduction when combined with vitamin C (250 mg/day). The benefits were not significantly associated with age, sex, aetiology of end-stage renal disease, serum electrolytes or HD duration, but showed a positive correlation ($P = 0.01$) with the type of therapy used.

According to one small study, vitamin E supplementation (500 mg/day) allowed for a reduction in erythropoietin dose (from 93 to 74 IU/kg/week) while maintaining stable haemoglobin concentrations (Cristol et al 1997).

Premenstrual syndrome (PMS)

Treatment with D-alpha-tocopherol (400 IU/day) over three menstrual cycles significantly alleviated some affective and physical symptoms of PMS according to one randomised double-blind study (London et al 1987). Symptoms of anxiety, food craving and depression responded to active treatment, whereas effects on other measured parameters such as weight gain were not significant.

An earlier study of 75 women with benign breast disease found that D-alpha-tocopherol (150–600 IU/day) significantly decreased some symptoms of PMS compared with a placebo; however, the study involved subjective patient evaluation, which may have influenced the findings (London et al 1983).

Dysmenorrhoea

According to two randomised placebo-controlled studies, taking 200 IU vitamin E twice daily or 500 IU daily, starting 2 days before menstruation and continuing for the first 3 days of bleeding, seems to reduce menstrual pain severity and duration and to decrease blood loss in teenaged girls with primary dysmenorrhoea (Ziaei et al 2001, 2005). Beneficial effects can be seen after 2 months and reach maximal effect after 4 months.

Intermittent claudication

A Cochrane Review of five placebo-controlled studies including a total of 265 volunteers (average age 57 years) concluded that, although further research is required to determine its effectiveness, vitamin E may have beneficial effects in intermittent claudication with no serious side effects (Kleijnen & Mackerras 2000). Treatment duration varied from 12 weeks to 18 months, and dosage regimens varied between the studies, which were considered generally small and of poor quality. A closer look at the evidence suggests that doses of at least 600 IU/day for a minimum of 12 weeks are required.

More recently, a randomised, double-blind study with vitamin E (400 IU/day) found no beneficial effects on perceived pain or treadmill-walking duration in people with claudication (Collins et al 2003).

A small study of 16 patients with stable claudication revealed that administration of vitamin E (200 mg/day) and vitamin C (500 mg/day) for 4 weeks reduces oxidative stress in this population,

and therefore may also have an effect on the remote ischaemia–reperfusion damage (Wijnen et al 2001).

Cancer

Most of the epidemiological evidence suggests that vitamin E and other antioxidants decrease the incidence of certain cancers. Based on these observations, numerous prospective and intervention studies have been conducted in various populations. Very often, vitamin E is used in combination with other antioxidant nutrients, and sometimes the form of tocopherol administered is not stated, thereby making it difficult to interpret study findings.

A review that systematically evaluated the scientific literature using guidelines developed by the US Preventative Services Task Force concluded that there is evidence to suggest that those individuals with higher serum vitamin E levels or who are receiving vitamin E supplementation have a decreased risk of some cancers, including lung, prostate, stomach and gastrointestinal carcinoma (Sung et al 2003). As can be expected, study design, differing treatment dose (nutritional levels or higher), form of vitamin used and population studied (general or high risk) had an influence on outcomes. Since then, several new studies have been published that cast doubt on the cancer protective effects of vitamin E for the general population. However, it seems likely that certain subpopulations (e.g. the poorly nourished) may benefit, and that lifestyle factors modify responses to supplementation (e.g. smoking). Recent research further suggests that differences in telomere length may be another factor affecting individuals' responses to vitamin E supplements (Shen et al 2009)

All cancers

A large study of nearly 30,000 subjects was carried out in Linxian, China. It tested four combinations of vitamins and minerals (retinol and zinc; riboflavin and niacin; vitamin C and molybdenum; and beta-carotene, vitamin E and selenium) over a 5-year period in a population with a persistently low intake of several micronutrients (Blot et al 1995). Although no statistically significant effect on cancer incidence was achieved by any intervention, secondary analysis showed that the combination of selenium, beta-carotene and alpha-tocopherol was associated with a statistically significant lower total mortality rate, a 13% reduction (borderline significant) in total cancer mortality rate and a statistically significant lower mortality rate from stomach cancer (a major cancer in Linxian).

Results from the SUVIMAX study suggest that protective effects of vitamin E may be gender specific (Zureik et al 2004). In this trial, antioxidant supplementation (vitamin C 120 mg, vitamin E 30 mg, beta-carotene 6 mg, selenium 100 micrograms, and zinc 20 mg) was associated with a lower cancer incidence in men, but not in women. It is possible that men in the SUVIMAX trial benefited from supplementation due to their lower baseline levels of antioxidants.

More recently four large studies have found that vitamin E supplementation has no protective effect against cancer incidence. The MRC/BHF study of 20,536 UK adults aged 40–80 years with coronary disease, other occlusive arterial disease, or diabetes found that a daily antioxidant supplement containing 600 mg vitamin E, 250 mg vitamin C and 20 mg beta-carotene produced no significant reduction in the incidence of cancer or in all-cause mortality (Parkinson Study Group 2002). The HOPE-TOO study, which used long-term natural vitamin E (400 IU/day) as a stand-alone supplement, failed to find a protective effect against cancer incidence or cancer deaths in people with preexisting vascular disease or diabetes mellitus (Lonn et al 2005). Long-term use of natural vitamin E (600 IU) taken on alternate days provided no overall benefit for cancer incidence or total mortality in a large randomised study involving 39,876 healthy women of at least 45 years of age (Lee et al 2005).

Results from 7627 women free of cancer at baseline in the Women's Antioxidant Cardiovascular Study (WACS) found that long-term use (average 9.4 years) of vitamin C (500 mg/day), natural vitamin E (600 IU every other day) and beta-carotene (50 mg every other day) was not significantly associated with lowered incidence of total cancer or cancer mortality for any of the tested antioxidants (O'Donnell et al 2009).

When data was evaluated for effects on site-specific cancers, women receiving vitamin E supplements had a reduced risk (but not statistically significant) for colorectal cancer compared with the placebo group. This was largely due to a reduced risk of colon cancer. However, there was no statistically significant association of vitamin E supplementation with rectal or other cancers. Further subgroup analysis revealed women in the vitamin E supplement group who currently smoked or had smoked in the past had lower rates of cancer death than those who never smoked.

Urinary tract cancer

Analysis of data from the ATBC Cancer Prevention Study, which tested synthetic vitamin E (50 mg/day) and beta-carotene (20 mg/day) in male Finnish smokers aged 50–69 years (n = 29,133) found neither supplement affected the incidence of urothelial cancer or the incidence of renal cell cancer (Virtamo et al 2000).

Aerodigestive cancers

Smoking and alcohol consumption are the major risk factors for upper aerodigestive tract cancers, and observational studies indicate a protective role for fruits, vegetables and antioxidant nutrients (Wright et al 2007). Analysis of data from the ATBC Cancer Prevention Study testing long-term supplementation with synthetic vitamin E (50 mg/day) and beta-carotene (20 mg/day) in male Finnish smokers aged 50–69 years (n = 29,133) found no effect of either agent on the overall incidence of any upper aerodigestive tract cancer nor any effect on mortality from these neoplasms.

Breast cancer

Mixed results have been obtained for vitamin E in the primary prevention of breast cancer, although a recent study has detected a modest protective

effect against recurrence of breast cancer and disease-related mortality in postmenopausal women previously diagnosed with the disease (Fleischauer et al 2003). Protective effects were established after 3 years' use, according to the study.

Ovarian cancer

Vitamin E supplements were protective against the incidence of ovarian cancer whereas consumption of antioxidants from diet was unrelated to risk according to another study (Fleischauer et al 2001). In analyses combining antioxidant intake from diet and supplements, vitamins C (> 363 mg/day) and E (> 75 mg/day) were associated with significant protective effects.

Colorectal cancer

Studies investigating the association between vitamin E and incidence of colorectal cancer have produced inconsistent results. Prospective studies have shown that high serum levels of vitamin E are protective; however, only one of three intervention studies has produced positive results (Stone & Papas 1997). These results are difficult to interpret, as the studies have been criticised for not adequately distinguishing between cancer incidence and adenoma recurrence.

In the WACS (n = 7627), women receiving natural vitamin E (600 IU every other day) had a reduced risk (but not statistically significant) of colorectal cancer compared with the placebo group. This was largely because of a reduced risk of colon cancer; however, there was no statistically significant association of vitamin E supplementation with rectal or other cancers (O'Donnell et al 2009). The ATBC study also detected a somewhat lower incidence of colorectal cancer in the alpha-tocopherol arm compared with the no alpha-tocopherol arm, but this was not statistically significant (Virtamo et al 2000).

Prostate cancer

The ATBC Cancer Prevention Study also provides information about the incidence of prostate cancer with long-term use of synthetic alpha-tocopherol (50 mg), beta-carotene (20 mg), both agents, or a placebo daily for 5–8 years (Albanes et al 2000). One of the most striking outcomes was a 32% decrease in the incidence of prostate cancer for volunteers receiving vitamin E (n = 14,564) compared to those not receiving it (n = 14,569) and a 41% reduction in mortality among men using vitamin E. Neither agent had any effect on the time interval between diagnosis and death (Heinonen et al 1998). The preventative effect of vitamin E on prostate cancer incidence was observed to be long term according to later analysis of postintervention effects (Virtamo et al 2003).

One study has identified a decrease in serum androgen concentrations associated with long-term alpha-tocopherol supplementation, suggesting this may be one of the factors contributing to the observed reduction in incidence and mortality of prostate cancer (Hartman et al 2001).

Currently, the US National Cancer Institute is conducting phases I, II and III chemoprevention trials for prostate, breast and colon cancers with vitamin E and the following micronutrients: isoflavones, lycopene, selenised yeast, selenomethionine, selenium, perillyl alcohol, folic acid, vitamin D, calcium and curcumin. It is suspected that the response to micronutrients may vary not only in magnitude but also in direction (Greenwald et al 2002).

Pancreatic cancer

Higher alpha-tocopherol concentrations may play a protective role in pancreatic carcinogenesis in male smokers according to the ATBC Cancer Prevention Study, which found men with the highest serum tocopherol levels had a lower pancreatic cancer risk (highest compared with lowest quintile) (Stolzenberg-Solomon et al 2009). Polyunsaturated fat, a putative pro-oxidant nutrient, modified the association such that the inverse alpha-tocopherol association was most pronounced in subjects with a high polyunsaturated fat intake. No associations were observed for dietary tocopherols and tocotrienols.

Other cancers

Further analysis of the ATBC Cancer Prevention Study found that neither synthetic vitamin E nor beta-carotene had a statistically significant effect on the rate of incidence of pancreatic carcinoma, the rate of mortality caused by this disease (Rautalahti et al 1999) or the occurrence of neoplastic changes in cases of atrophic gastritis (Varis et al 1998).

Adjunct with cisplatin

Bove et al (2001) made the observation that the neurotoxic presentation associated with cisplatin use was similar to that of vitamin E deficiency. They hypothesised that cumulative cisplatin use could induce vitamin E deficiency if patients' levels were not sufficiently high throughout treatment. To test the theory they started by measuring vitamin E in the plasma of five patients who developed severe neurotoxicity after cisplatin treatment and in another group of five patients before and after two or four cycles of cisplatin treatment. This produced preliminary data that supported the theory that inadequate vitamin E due to cisplatin treatment could be responsible for the peripheral nerve damage induced by free radicals (Bove et al 2001). Following this, four clinical trials were conducted to evaluate whether oral vitamin E supplementation could reduce the incidence of cisplatin-induced neurotoxicity. In all trials the incidence of chemotherapy-induced peripheral neuropathy was significantly reduced with vitamin E supplementation (Wolf et al 2008).

Oral vitamin E (300 mg/day), taken before cisplatin treatment and continued for 3 months after cessation of treatment, significantly reduced the incidence and severity of neurotoxicity according to a randomised study (n = 47), in which the incidence of neurotoxicity was significantly lower in the group receiving vitamin E (30.7%) compared to those receiving the placebo (85.7%; $P < 0.01$) (Pace et al 2003). Shortly afterwards, Argyriou et al (2005) conducted a randomised study of 31 patients

with cancer treated with six courses of cumulative cisplatin, paclitaxel or their combination regimens. Only 25% of patients randomly assigned to receive oral vitamin E (600 mg/day) during chemotherapy and for 3 months after its cessation developed neurotoxicity, compared to 73% in the control group. A year later in another randomised study, 30 patients scheduled to receive six courses of cumulative cisplatin-based regimens were randomly allocated to receive either vitamin E (600 mg/day) during chemotherapy and for 3 months after its cessation or no adjunctive therapy (controls). This study again found a significantly reduced incidence of neurotoxicity with vitamin E (21.4%) compared to controls (68.5%) ($P = 0.026$) (Argyriou et al 2006).

While no data was included on the long-term survival of the patients involved, studies undertaken have failed to show a detrimental effect from combining vitamin E with chemotherapy (Ladas et al 2004, Pace et al 2003). The results of these studies are promising in the chemotherapy setting.

Arthritis

High-dose vitamin E supplements may be effective in relieving pain in osteoarthritis (OA) and rheumatoid arthritis (RA), according to several double-blind studies, with some studies finding that the effects are as strong as with diclofenac. Vitamin E supplements have been studied in people with OA, RA, spondylitis ankylosis, spondylosis and psoriatic arthritis. Comparisons have been made to placebos and NSAIDs.

Osteoarthritis

According to an early crossover study (Machtey & Ouaknine 1978), 52% of OA patients experienced less pain when treated with vitamin E (600 mg/day) compared to a placebo. Several years later, a double-blind randomised study of 50 volunteers with OA confirmed these findings and showed that vitamin E (400 IU/day) was significantly superior to a placebo in relieving pain, increasing mobility and reducing analgesic requirements (Blankenhorn 1986). Symptoms of pain at rest, during movement or with applied pressure all responded to treatment with vitamin E.

Vitamin E supplementation (500 IU/day) did not alter the loss of cartilage volume in knee OA according to a 2-year, double-blind, randomised, placebo-controlled study of 138 patients (American College of Rheumatology clinical and radiographic criteria) (Wluka et al 2002). Additionally, symptoms did not improve. Vitamin E also failed to alleviate symptoms in a shorter, 6-month double-blind study using the same dose (Brand et al 2001) and symptoms of pain, stiffness and function did not change at the 1-, 3- or 6-month assessments.

Research has continued in recent years, so that by 2007 a systematic review by Canter, Wider and Ernst (2007) identified a total of seven RCTs that have tested vitamin E in OA: four trials compared the treatment with a placebo, two tested against diclofenac and one against vitamin A. Of these, two placebo-controlled trials demonstrated the effectiveness of vitamin E for pain. One trial was considered methodologically weak, but the second was more robust and indicated greater effectiveness both for the whole patient sample and for a subgroup with OA of the knee and hip. This is in contrast to two later studies that involved patients with OA of the knee and produced largely negative results. Two equivalence trials comparing vitamin E to diclofenac produced more positive outcomes and suggested similar effectiveness for the two treatments, with one study reporting a statistically significant superiority of vitamin E over diclofenac (Canter et al 2007). The authors of the review have claimed variable methodological rigour does not yet allow a definitive conclusion to be made about the effectiveness of vitamin E in OA.

Rheumatoid arthritis

According to several double-blind studies, a dose of 1200 mg/day vitamin E significantly reduces pain symptoms in people with RA, but not always morning stiffness.

A double-blind study of 42 RA patients who received vitamin E (600 mg twice a day) over 12 weeks showed that pain parameters were significantly decreased with active treatment compared to a placebo (Edmonds et al 1997). The same study also found no change in the Ritchie Articular Index, duration of morning stiffness, swollen joint count or laboratory parameters with vitamin E supplementation compared to a placebo. A further study using the same dose detected a significant inverse correlation between vitamin E levels and pain score, whereas morning stiffness and sedimentation rate were not affected (Scherak & Kolarz 1991).

Edmonds et al enrolled 42 patients with RA in a double-blind randomised study in which alpha-tocopherol (600 mg twice a day) was compared to a placebo for 12 weeks (Edmonds et al 1997). While laboratory measures of inflammatory activity and oxidative modification were unchanged with active treatment, pain parameters were significantly decreased after vitamin E treatment when compared with the placebo, suggesting that vitamin E may exert a small but significant analgesic activity independent of a peripheral anti-inflammatory effect.

More recently, a combination of standard treatment (intramuscular methotrexate, oral sulfasalazine and indomethacin suppository at night) and vitamin E (400 mg three times daily) was compared to standard treatment and a combination of antioxidants or to standard treatment alone (Helmy et al 2001). Standard treatment started to produce tangible improvements after 2 months, whereas additional treatment with either vitamin E or antioxidants improved symptoms more quickly (after 1 month).

Comparisons with pharmaceutical medication

After 3 weeks' treatment with either high-dose vitamin E (400 mg RRR-alpha-tocopherol acetate three times daily) or diclofenac sodium, a significant improvement in all assessed clinical parameters was observed in hospitalised patients with established chronic RA ($n = 85$), according to a randomised, double-blind parallel group trial (Wittenborg et al

1998). Duration of morning stiffness, grip strength and the degree of pain, assessed by a 10 cm visual analogue scale, reduced significantly with vitamin E as well as with diclofenac. Both treatments were considered to be equally effective by patients and physicians.

Menopausal symptoms

According to a review published by the Mayo Clinic in the USA, behavioural changes in conjunction with vitamin E (800 IU/day) is a reasonable initial approach for menopausal women with mild symptoms that do not interfere with sleep or daily function (Shanafelt et al 2002). The recommendation is based on a double-blind, randomised, placebo-controlled, crossover clinical trial that found that vitamin E (800 IU/day) was more effective than a placebo in controlling hot flushes in breast cancer survivors. Benefits have been confirmed in another double-blind, placebo-controlled trial, which found treatment with 400 IU vitamin E daily significantly reduced hot flush severity and daily frequency as reported by participants (Ziaei et al 2007).

Male infertility

Lipid-soluble antioxidants such as vitamin E have been studied for their effects in male reproductive physiology because the membranes of germ cells and spermatozoa are very sensitive to oxidation (Bhardwaj et al 2000, Bolle et al 2002).

According to three of four studies, oral vitamin E supplementation can effectively treat some forms of male infertility (Geva et al 1996, Kessopoulou et al 1995, Rolf et al 1999, Suleiman et al 1996). Doses varied from 200 mg/day to 800 mg/day.

Kessopoulou et al (1995) compared vitamin E (600 mg/day) to a placebo over 3 months in 30 healthy men with high levels of ROS generation in semen and a normal female partner. The randomised, crossover study found active treatment improved zona binding, thereby showing that vitamin E significantly improved the in vitro function of human spermatozoa. Geva et al (1996) studied men enrolled in an in vitro fertilisation program that previously had low fertilisation rates, and treated them with oral vitamin E (200 mg/day) for 3 months. After the first month, fertilisation rates increased significantly, from 19% to 29%. The same year, Suleiman et al (1996) treated asthenospermic patients with oral Vitamin E, which significantly decreased the malondialdehyde (MDA) concentration in spermatozoa and improved sperm motility. Of the 52 treated males, 11 (21%) impregnated their spouses and 9 of the spouses successfully continued to have normal-term deliveries, whereas two aborted in the first trimester. No pregnancies were reported in the spouses of the placebo-treated patients.

The negative study used high-dose oral vitamin C (1000 mg/day), and vitamin E (800 mg/day) was tested over 56 days in 31 men with asthenozoospermia (< 50% motile spermatozoa) and normal or only moderately reduced sperm concentration ($> 7 \times 10^6$ spermatozoa/mL) (Rolf et al 1999).

Dermatological conditions

Vitamin E is used both as an oral supplement and as a topical preparation in a variety of dermatological conditions. It is a popular ingredient in many moisturising preparations used to: alleviate dry and cracked skin; assist in the repair of abrasions, burns, grazes and skin lesions; prevent stretch marks; and diminish scar tissue. Vitamin E oil is used as a stand-alone preparation or incorporated into a cream or ointment base for these purposes.

Sunburn protection

Topical application of 1% alpha-tocopherol provided significant protection against erythema and sunburn in an experimental model. When combined with 15% ascorbic acid, the protective effect was enhanced (Lin et al 2003). Further improvements were seen when ferulic acid was added to the alpha-tocopherol (1%) and ascorbic acid (15%) solution, as this substance improves chemical stability of the antioxidants and doubles the photoprotective effect (Lin et al 2005).

Once again, it appears that not all forms of vitamin E exert a significant protective effect (McVean & Liebler 1999). According to an in vivo study, a 5% dispersion of alpha-tocopherol, gamma-tocopherol or delta-tocopherol in a neutral cream vehicle produced a statistically significant inhibition of thymine dimer formation, whereas alpha-tocopherol acetate and alpha-tocopherol methyl ether had no effect. Further research revealed that gamma-tocopherol and delta-tocopherol were five- to ten-fold less potent than alpha-tocopherol (McVean & Liebler 1997).

A comparison between topical vitamins E and C has demonstrated that vitamin E affords better protection against UVB radiation, whereas vitamin C is superior against UVA radiation (Baumann & Spencer 1999).

Although most research has focused on topical use, oral administration of a combination of high-dose vitamins E and C increases the threshold to erythema. The first study to show that the systemic administration of vitamins E and C reduces the sunburn reaction in humans was a small, double-blind, placebo-controlled trial that used ascorbic acid (2 g/day) combined with D-alpha-tocopherol (1000 IU/day) (Eberlein-Konig et al 1998). The effect was seen after 8 days. The next to show reduction of the sunburn reaction was a 50-day study of 40 volunteers (20–47 years old), which showed that supplemental vitamin E (2 g/day) and C (3 g/day) protected against sunburn and resulted in increased vitamin E levels in keratinocytes (Fuchs & Kern 1998). This was once again confirmed in a controlled study of 45 healthy volunteers (Mireles-Rocha et al 2002). The doses used were lower in this study: 1200 IU/day of D-alpha-tocopherol in combination with vitamin C (2 g/day).

Scar tissue

Although vitamin E is widely used to diminish the appearance of scars, a small double-blind study of 15 patients who had undergone skin cancer removal found that applying an emollient preparation known

as Aquaphor with added vitamin E after surgery either had no effect or worsened the appearance of scars compared to Aquaphor alone (Baumann & Spencer 1999). A larger study of 80 people with hypertrophic scars and keloids found that treatment with vitamin E and silicone gel sheets was successful in scar treatment (Palmieri et al 1995). After 2 months, 95% of patients receiving vitamin E and gel sheet treatment had improved by 50%, whereas 75% had improved by 50% without vitamin E.

Type 1 diabetes

Although the Heart Outcomes Prevention Evaluation (HOPE) study involving 3654 people with diabetes failed to detect a preventative effect for long-term vitamin E (400 IU/day) on cardiovascular disease outcomes or nephropathy, other studies have identified that long-term treatment improves metabolic control in type 1 diabetes and may be useful to reduce oxidative stress (Jain et al 1996, Lonn et al 2002).

Chronic hepatitis C

According to a 2004 systematic review, significant improvements in biochemical responses were seen for vitamin E compared to a placebo (Coon & Ernst 2004). They report on one placebo-controlled trial in which a statistically significant reduction in liver enzyme (ALT) was observed during vitamin E treatment but reductions were not consistent for all patients and complete normalisation of ALT levels did not occur.

Asthma and atopy

Studies have consistently demonstrated beneficial associations between dietary vitamin E and ventilatory function, and a few have demonstrated beneficial associations with asthma and atopy (Devereux & Seaton 2005). However, benefits do not extend to vitamin E supplements, as a recent randomised study ($n = 72$) using natural vitamin E (500 mg/day) over 6 weeks found no clinical benefit in subjects with mild to moderate asthma (Pearson et al 2004).

Age-related macular degeneration (AMD)

According to a review of randomised trials comparing antioxidant vitamin and/or mineral supplement to controls, there is no evidence that antioxidant (vitamin E or beta-carotene) supplementation prevents AMD. However, there is evidence that supplementation with antioxidants (beta-carotene 15 mg, vitamin C 500 mg and vitamin E 400 IU) and zinc (elemental 80 mg) daily slows down the progression to advanced AMD and visual acuity loss in people with signs of the disease (Evans 2008). People with AMD, or early signs of the disease, may experience some benefit from taking supplements as used in the ARED trial (Sackett & Schenning 2002).

Huntington's disease

Vitamin E supplementation may slow the rate of motor decline early in the course of Huntington's disease, according to a randomised, double-blind, placebo-controlled study of high-dose D-alpha-tocopherol treatment (Peyser et al 1995). The study of 73 patients with Huntington's disease found that treatment with D-alpha-tocopherol had no effect on neurologic and neuropsychiatric symptoms in the treatment group overall; however, post hoc analysis revealed a significant selective therapeutic effect on neurologic symptoms for patients early in the course of the disorder.

OTHER USES

Oral supplements have been used to prevent or treat many other conditions such as exercise-induced tissue damage, some types of senile cataracts, epilepsy and fibromyalgia.

Vitamin E prophylaxis in premature babies significantly reduces the risk of stage 3+ retinopathy by 52%, according to a 1997 meta-analysis of six randomised studies (Raju et al 1997).

Infusions of vitamin E are being investigated as a means of preventing ischaemic reperfusion injury in liver and heart surgery (Bartels et al 2004, Jaxa-Chamiec et al 2005).

DOSAGE RANGE

The body's requirement for vitamin E changes according to the amount and type of fat eaten in the diet. For example, vitamin E requirements increase when there is a high intake of PUFAs (Wahlqvist 2002).

Many scientists believe it is difficult for an individual to consume more than 15 mg/day of alpha-tocopherol from food alone, without also increasing fat intake above recommended levels.

Recommendations for adults (Australian adequate intake)

- Men > 18 years: 10 mg/day alpha-tocopherol.
- Women > 18 years: 7 mg/day alpha-tocopherol.
- Upper level of intake: 300 mg/day alpha-tocopherol.
- Deficiency treatment: 800–1200 mg/day.

According to clinical studies

Both natural and synthetic forms of vitamin E have been evaluated in clinical trials at different doses and durations, and sometimes in combination with other nutrients that also exhibit antioxidant properties. Unless stated, dosages are for natural vitamin E (alpha-tocopherol).

- Alzheimer's disease: 2000 IU/day synthetic alpha-tocopherol.
- Anaemia in haemodialysis: 500 mg/day.
- Angina pectoris: 50–300 mg/day.
- Antioxidant effects: 400 IU/day.
- Cancer, to reduce cisplatin-induced neurotoxicity: oral vitamin E (600 mg/day) during chemotherapy and for 3 months after its cessation.
- Cerebral infarction prevention: 50 mg/day synthetic vitamin E.
- Colorectal cancer prevention: 50 mg/day long term.
- Cardiovascular disease primary prevention: 100–260 IU/day long term.
- Cardiovascular disease secondary prevention: 100–800 IU/day long term.

- Carotid atherosclerosis, slowing progression: 136 IU twice daily and vitamin C 250 mg (slow release) twice daily.
- Dementia prevention: 400 IU/day alpha-tocopherol plus vitamin C 500 mg/day.
- Haemodialysis, associated cramps: 400 mg/day alpha-tocopherol plus vitamin C 250 mg/day.
- Hypertension: 200 IU/day long term.
- Immune system support in the elderly: 200 mg/day.
- Intermittent claudication: 600–1600 IU/day.
- Ischaemic stroke prevention in high-risk hypertension: 50 mg/day.
- Male infertility: 200–800 mg/day.
- Menopausal symptoms: 800 IU/day.
- Nitrate tolerance prevention: 200 mg three times daily.
- Osteoarthritis: 1200 IU/day.
- Ovarian cancer: > 75 mg/day.
- Premenstrual symptoms: 400–600 IU/day.
- Prostate cancer prevention: 50 mg/day.
- Retinopathy of prematurity: 100 mg/kg/day.
- Rheumatoid arthritis: 1200 IU/day.
- Sunburn protection: 1000 IU/day up to 2000 mg/day plus vitamin C 2000–3000 mg/day.

TOXICITY

Vitamin E is relatively non-toxic. It is not stored as readily in the body as other fat-soluble vitamins and up to 60–70% of a daily dose is excreted in the faeces. Doses as high as 3200 mg/day have been used for 12 years with few adverse effects (Fariss & Zhang 2003).

In April 2000, the Food and Nutrition Board of the Institute of Medicine in the United States set an upper tolerable limit of 1500 IU of RRR-alpha-tocopherol as the highest dose unlikely to result in haemorrhage in most adults.

ADVERSE REACTIONS

Adverse effects are dose related and tend to occur only at very high supplemental doses (> 1200 IU/day); they include diarrhoea, flatulence, nausea and heart palpitations. Doses above this level should be used only under professional supervision.

SIGNIFICANT INTERACTIONS

Considering vitamin E is a fat-soluble vitamin, any medication that reduces the absorption of fats in the diet will also reduce the absorption of vitamin E. These include cholestyramine, colestipol, isoniazid, mineral oil, orlistat and sucralfate.

Chloroquine

According to in vitro research, vitamin E inhibits drug uptake in human cultured fibroblasts. The clinical significance of this observation is unknown. Observe patients taking this combination (Scuntaro et al 1996).

Chlorpromazine

According to in vitro research, vitamin E inhibits drug uptake in human cultured fibroblasts. The clinical significance of this observation is unknown — observe patients taking this combination (Scuntaro et al 1996).

Cisplatin

A review of four clinical trials testing the effects of the combination of vitamin E with cisplatin has shown that in all trials the incidence of chemotherapy–induced peripheral neuropathy was significantly reduced (Wolf et al 2008). Beneficial interaction, but should be used under professional supervision.

Warfarin

Contradictory results have been obtained in clinical studies that have investigated whether vitamin E affects platelet aggregation or coagulation. A dose of 1200 IU/day (800 mg of D-alpha-tocopherol) taken for 28 days had no effects on platelet aggregation or coagulation according to one clinical study (Morinobu et al 2002). Similarly, a second clinical study found that a lower dose of 600 mg (900 IU) of RRR-alpha-tocopherol taken daily for 12 weeks did not alter coagulation activity (Kitagawa & Mino 1989). In contrast, increased risk of gingival bleeding at doses of 50 mg/day was found by another study (Liede et al 1998).

Overall, it appears that people with reduced levels of vitamin K may be more susceptible to the effects of vitamin E, potentiating warfarin activity. Until further research can clarify whether the interaction is clinically significant for most people, it is recommended that prothrombin time ratio, or INR, should be closely monitored upon the addition and withdrawal of treatment with high-dose vitamin E supplements.

Doxorubicin

One study found that oral DL-alpha-tocopheryl acetate (1600 IU/day) prevented doxorubicin-induced alopecia (Wood 1985). The same dose of oral DL-alpha-tocopheryl acetate failed to prevent alopecia after doxorubicin treatment following mastectomy for breast cancer (Martin-Jimenez et al 1986). It also failed to prevent alopecia in a second study of 20 patients with different types of solid tumours (Perez et al 1986). Possible beneficial interaction but difficult to assess.

Nitrates

Oral vitamin E prevented nitrate tolerance when given concurrently with transdermal nitroglycerin (10 mg/24 hours), according to one randomised placebo-controlled study (Watanabe et al 1997). Beneficial interaction possible.

NSAIDs and simple analgesics

Vitamin E may enhance the pain-modifying activity of drugs. Beneficial interaction possible; drug dosage may require modification.

Propranolol

According to in vitro research, vitamin E inhibits drug uptake in human cultured fibroblasts. The clinical significance of this observation is unknown. Observe patients taking this combination (Scuntaro et al 1996).

PRACTICE POINTS/PATIENT COUNSELLING

- Vitamin E is actually a generic term used to describe any chemical entity that displays the biological activity of RRR-alpha-tocopherol, the most abundant form found in nature. The 'natural' form is the most potent of all eight forms of vitamin E, although there is evidence that other tocopherols also exhibit significant beneficial effects.
- It is involved in myriad biochemical processes such as immunocompetence and neurological function, but its most important biological function is that of an antioxidant.
- Vitamin E is used for many different indications. There is evidence to suggest that supplementation may be useful in:
  - secondary cardiovascular disease prevention, although effects are inconsistent
  - slowing down progression of Alzheimer's dementia, although effects are inconsistent
  - enhancing immune function in the elderly
  - preventing anaemia and treating cramps in patients on haemodialysis
  - reducing PMS, dysmenorrhoea and menopause symptoms
  - reducing pain in OA and RA
  - improving some forms of male infertility
  - reducing risk of stage 3+ retinopathy in premature babies
  - preventing ischaemic stroke in high-risk hypertensive patients
  - reducing incidence of some cancers, although effects are inconsistent
  - preventing sunburn (when used with vitamin C)
  - slowing down carotid atherosclerosis (when used with vitamin C)
  - reducing blood pressure
  - reducing nitrate tolerance
  - reducing cisplatin-induced neurotoxicity.
- Oral supplements have been used to prevent or treat many other conditions, such as exerciser-induced tissue damage, some types of senile cataracts, epilepsy and fibromyalgia.
- It is a popular ingredient in many moisturising preparations used to: alleviate dry and cracked skin; assist in the repair of abrasions, burns, grazes and skin lesions; prevent stretch marks; and diminish scar tissue. Vitamin E oil is used as a stand-alone preparation or incorporated into a cream or ointment base for these purposes.
- People with impaired coagulation, inherited bleeding disorders, a history of haemorrhagic stroke or vitamin K deficiency, or who are at risk of pulmonary embolism or thrombophlebitis should use high-dose supplements under medical supervision.

CONTRAINDICATIONS AND PRECAUTIONS

Vitamin E is considered to be a safe substance.

People with impaired coagulation, inherited bleeding disorders, a history of haemorrhagic stroke, vitamin K deficiency or at risk of pulmonary embolism or thrombophlebitis should use high-dose supplements under medical supervision.

Although it was thought that people with hypertension wanting to take supplements should start with low doses, evidence does not support the concern that high-dose supplements will significantly elevate blood pressure. Suspend use of high doses (> 1000 IU/day) 1 week before major surgery.

PREGNANCY USE

Vitamin E is considered to be safe in pregnancy.

PATIENTS' FAQs

What will this vitamin do for me?

Vitamin E is essential for health and wellbeing. It is involved in many important biological processes in the body and may prevent serious diseases such as heart disease and some cancers; however, people with these conditions should seek professional advice. It is also used to reduce symptoms in common conditions such as arthritis, PMS and menopause. Vitamin E supplements enhance immune function in the elderly and may slow the progression of Alzheimer's dementia, although this is still not conclusive. Oral supplements have been used to prevent or treat many other conditions such as exercise-induced tissue damage, some types of senile cataracts, epilepsy and fibromyalgia.

When will it start to work?

This depends largely on the reason for taking the supplement. In the case of disease prevention, studies suggest that long-term use is necessary (i.e. 2–3 years or longer). When using vitamin E to reduce symptoms, effects have generally been seen within 3 months.

Are there any safety issues?

People with impaired coagulation, inherited bleeding disorders, a history of haemorrhagic stroke or vitamin K deficiency, or who are at risk of pulmonary embolism or thrombophlebitis should use high-dose supplements under medical supervision. Additionally, vitamin E can interact with some medicines, so professional advice is recommended when using high-dose supplements.

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Wild yam

HISTORICAL NOTE Wild yams have made a significant contribution as a root crop to tribal people in some parts of the world, such as Nepal. They are usually consumed boiled, steamed, baked or fried. Many different forms and cultivars of the wild edible yam species are available in different areas, and it is likely that these differ in composition and nutritional values. Traditionally, wild yams have also been used as medicine and are believed to exert antispasmodic, anti-inflammatory and autonomic nervous system relaxant effects. Wild yam is a source of diosgenin, the raw material originally used to produce progesterone in the laboratory.

COMMON NAME
Wild yam

OTHER NAMES
Atlantic yam, barbasco, China root, colic root, devil's bones, Mexican yam, natural DHEA, rheumatism root, wild Mexican yam, yuma

BOTANICAL NAME/FAMILY
Discorea composita, *D. floribunda*, *D. mexicana*, *D. macrostachya*, *D. villosa* (family Dioscoreaceae [yams])

PLANT PART USED
Root and rhizome

CHEMICAL COMPONENTS
The root of the wild yam contains diosgenin, dioscin, dioscorin and a range of vitamins and minerals such as vitamin C, beta-carotene, vitamins B_1, B_2 and B_3, iron, magnesium, potassium, selenium and zinc (USDA 2003), along with polyphenols (Bhandari & Kawabata 2004). Although diosgenin can be converted to dihydroepiandosterone (DHEA) and other steroid compounds in the laboratory, and has been used for commercial production of these compounds, this conversion does not occur in the human body. Additionally, wild yam does not contain progesterone or any other active steroid hormones.

MAIN ACTIONS

Hormonal actions
The evidence of a hormonal action with wild yam varies. Wild yam extract may enhance oestradiol binding to oestrogen receptors and induce transcription activity in oestrogen-responsive cells (see wild yam at http://www.naturaldatabase.com), and diosgenin has been observed to have an oestrogenic action on mouse mammary epithelium (Aradhana & Kale 1992). In contrast, in an oestrogen competition assay using human breast cancer cell, diosgenin was found to cause an acute, endothelium-independent coronary artery relaxation, but did not interact with oestrogen or progesterone receptors (Au et al 2004), and extracts with an upper limit of 3.5% diosgenin have been found to have no oestrogenic activity (Hooker 2004).

One study looking at steroid-hormone-regulated gene expression using an in vitro tissue-culture indicator system suggests that wild yam extract does not have significant oestrogenic or progesteronal activity, but rather weak anti-oestrogenic and/or anti-androgenic activities (Rosenberg Zand et al 2001). A further study suggests that wild yam extract suppresses progesterone synthesis without direct effects on oestrogen or progesterone receptors (Zava et al 1998). In an in vivo study, supplementation with diosgenin protected the kidney from morphological changes associated with ovariectomy (Tucci & Benghuzzi 2003) and produced a significant decrease in the cortical and medullary adrenal areas of ovariectomised rats (Benghuzzi et al 2003).

There is in vitro evidence that diosgenin upregulates vascular endothelial growth factor-A and promotes angiogenesis in pre-osteoblast-like cells via pathways involving oestrogen receptors (Men et al 2005).

Cholagogue
There appears to be more consistent evidence for wild yam's effect on bile flow. Diosgenin has been shown to increase biliary secretion of cholesterol (Accatino et al 1998, Yamada et al 1997) and prevent oestrogen-induced bile flow suppression in rats (Accatino et al 1998), as well as increase elimination of indomethacin and reduce indomethacin-induced intestinal inflammation (Yamada et al 1997).

OTHER ACTIONS
Traditionally, wild yam is also believed to exert antispasmodic, anti-inflammatory and autonomic nervous system relaxant effects (Fisher & Painter 1996). Wild yam exhibits significant antioxidant activity (Bhandari & Kawabata 2004).

Clinical note — The major influence of wild yam on modern medicine

The Mexican wild yam has had a major influence on drug development and modern medical practice, although few people are familiar with the story and misunderstandings abound.

In the late 1930s scientists entering the field of sex endocrinology were confronted with the sober reality that they were dealing with research materials (animal glands) that needed to be sourced from slaughterhouses and were not readily available in sufficient quantities (Soto Laveaga 2005). Eventually, female urine was identified as a better source of hormones and provided an alternative. As pharmaceutical companies embarked upon large-scale hormone production, it became apparent that a cheaper and more abundant source of raw materials would need to be found; hence, a search through the plant kingdom ensued.

The American chemist Russell Marker identified that saponins in plants could be chemically modified to produce steroids and that sex hormones could be synthesised using yams (Soto Laveaga 2005). For several years he tried unsuccessfully to direct pharmaceutical companies to use Mexico as a source of wild yams, but the general perception was that Mexico was too politically unstable and unsophisticated. Over time, changes in the infrastructure of the Mexican countryside coincided with further chemical discoveries, and wild yam root picking became a financial panacea to previously unemployed peasants in yam-rich areas. By the 1950s, scientists at the pharmaceutical company Upjohn had found a way to convert diosgenin to progesterone, then to hydrocortisone and finally cortisone, thereby reinforcing the importance of wild yam as a source of raw materials for steroid drugs. Considering the importance of these events, it could be said that wild yams revolutionised the world of modern medicine.

At one stage Mexican wild yams provided up to 90% of the world's raw material for steroid drug synthesis, but this has steadily fallen owing to the rapid increase in demand for larger quantities and Mexico's reduced ability to produce wild yam tubers (Soto Laveaga 2005).

CLINICAL USE

The therapeutic effectiveness of wild yam has not been significantly investigated under clinical trial conditions, so evidence is derived from traditional, in vitro and animal studies.

Menopausal symptoms and other female reproductive conditions

Although wild yam is a popular treatment for menopausal symptoms, there is currently no clinical research supporting its use for these indications.

Wild yam has been used as a 'natural alternative' to oestrogen replacement therapy, to treat postmenopausal vaginal dryness, PMS and osteoporosis, and to increase energy and libido in men and women, as well as for breast enlargement. The use of wild yam as a natural progesterone appears misguided, because diosgenin is not converted to progesterone, DHEA or other steroid hormones in vivo. One small, double-blind, placebo-controlled crossover trial of topical wild yam extract showed no effect on menopausal symptoms (Komesaroff et al 2001). The study involved 23 healthy women suffering from troublesome menopause symptoms. After a 4-week baseline period, each woman was randomly assigned the active cream and matching placebo for 3 months. No changes in body weight, SBP or DBP, levels of total serum cholesterol, triglyceride, HDL-cholesterol, FSH, glucose, oestradiol, or serum or salivary progesterone were detected after 3 months' treatment.

OTHER USES

Wild yam has been used traditionally as an antispasmodic for treating diverticulosis, gall bladder colic, painful menstruation, cramp, nausea in pregnancy and rheumatoid arthritis, and for increasing energy (Fisher & Painter 1996). It may also be useful when combined with other herbs for irritable bowel syndrome (Abascal & Yarnell 2005).

DOSAGE RANGE

- Decoction of dried root: 2–4 g three times daily.
- Tincture (1:5): 2–10 mL three times daily.
- Liquid extract (1:2): 3–6 mL/day.

TOXICITY

Considering that wild yams are widely consumed as food by several tribal groups, it appears that dietary ingestion is non-toxic. After assessment with short-term toxicity tests, dermal irritation tests, a sensitisation test, an ocular irritation test, a rat uterotropic assay and genotoxicity tests, wild yam was deemed safe for use in cosmetic products (Hooker 2004).

ADVERSE REACTIONS

In large doses, wild yam may cause nausea, vomiting and diarrhoea.

SIGNIFICANT INTERACTIONS

Insufficient reliable data are available to determine whether interactions may occur.

CONTRAINDICATIONS AND PRECAUTIONS

None known.

PREGNANCY USE

Likely to be safe when consumed in dietary amounts; however, safety is not known when used in larger quantities.

PATIENTS' FAQs

What will this herb do for me?

Although the herb is used medicinally to treat menopausal symptoms, there is no scientific evidence to support this.

When will it start to work?

This cannot be answered based on scientific evidence.

Are there any safety issues?
Given that it is consumed as food, usual dietary intakes may be considered safe.

PRACTICE POINTS/PATIENT COUNSELLING
- Wild yam is a popular root vegetable in some parts of the world.
- It is also a popular ingredient in commercial herbal formulas developed for menopausal women.
- Wild yam has been touted as having progesteronal and/or oestrogenic activity, but current evidence suggests this is unlikely.
- There is no clinical or scientific evidence to support the use of wild yam in the treatment of conditions of the female reproductive system.
- Wild yam root may be useful as an antispasmodic. Its use as a source of naturally occurring sex hormones appears misguided.

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Willowbark

HISTORICAL NOTE This herb has been used as a therapeutic agent since ancient times, with some reports of its use around 500 BC in ancient China as a treatment for pain and fever, and around 400 BC by Hippocrates, who recommended the bark be chewed for relief of fever and pain. As centuries passed, herbalists continued to prescribe the bark for many conditions, and by the 18th century it was widely used as an antipyretic and analgesic. During the late 1820s, French and German scientists extracted the glycosidic constituents, including salicin (Hedner & Everts 1998). The oxidation of salicin yields salicylic acid, which was produced in the mid 1800s but had limited clinical use due to the gastric irritation it caused. In 1853 a French chemist neutralised salicylic acid to create acetylsalicylic acid, but had no interest in marketing it and abandoned his discovery. A Bayer chemist called Hoffmann rediscovered acetylsalicylic acid in 1897 as a better tolerated treatment for his father's rheumatoid arthritis and within 2 years it was marketed by Bayer under the tradename of Aspirin (Setty & Sigal 2005). Since then it has become one of the most successful medicines in history. Although many believe aspirin was synthesised from the salicin found in willowbark, it was actually the salicin found in another herb, meadowsweet, from which aspirin was developed.

OTHER NAMES

White willowbark, brittle willow, bay willow, crack willow, purple willow, silberweide, violet willow

While white willow (*Salix alba*) is the willow species most commonly used for medicinal purposes, crack willow (*S. fragilis*), purple willow (*S. purpurea*) and violet willow (*S. daphnoides*) are all salicin-rich and are sometimes sold under the label of willow bark (Setty & Sigal 2005).

BOTANICAL NAME/FAMILY

Salix alba (family Salicaceae)

PLANT PART USED

Bark

CHEMICAL COMPONENTS

Phenolic glycosides (mainly salicylates including salicin and its derivatives), tannins (mainly catechin tannins, some gallontannins and condensed tannins [procyanidins]), lignans and flavonoids.

MAIN ACTIONS

Anti-inflammatory and analgesic

Clinical studies using willowbark preparations standardised to salicin content have shown anti-inflammatory and analgesic activity (Chrubasik et al 2000, 2001a, 2001b, Mills et al 1996, Schmid et al 2000). In vitro studies have demonstrated that *Salix* extract inhibits COX-2-mediated PGE_2 release and that it is a weak inhibitor of pro-inflammatory cytokines (Fiebich & Chrubasik 2004). While salicin is considered the main analgesic constituent, it is now thought that other constituents such as tannins, flavonoids and salicin esters may contribute to its overall effect (Schmid et al 2001).

CLINICAL USE

In clinical practice, willowbark is generally used as a symptomatic treatment in osteoarthritic conditions and lower back pain. Of the five RCTs conducted to investigate its effects in these conditions, all but one have produced positive results (Biegert et al 2004, Chrubasik et al 2000, 2001a, Mills et al 1996, Schmid et al 2000).

Joint pain and inflammation

Osteoarthritis

Four randomised double-blind trials have investigated the efficacy of willowbark in people with osteoarthritis, with the two earlier studies finding that herbal treatment produced symptom-relieving effects superior to a placebo (Biegert et al 2004, Mills et al 1996, Schmid et al 2000). Seventy-eight subjects were randomly assigned willowbark extract (240 mg salicin/day) or a placebo over a 2-week period, after which active treatment was found to produce a statistically significant improvement (Schmid et al 2000). Mills et al (1996), testing willowbark in 82 patients with chronic arthritic pain, also found active treatment produced a statistically significant alleviation of pain symptoms. The effectiveness and tolerance of willowbark extract compared to conventional therapies was tested in patients with knee or hip pain in a cohort study with a control group. This open, observational study included 90 patients treated with a standardised willowbark extract preparation (equivalent to 240 mg salicin daily), and a reference group of 41 patients with a standard therapy prescribed by a doctor and 8 patients with a combination of the two. Both the doctors and the patients judged the effectiveness in both groups to be comparable. After 6 weeks, the effectiveness and tolerance of the willowbark extract was better than conventional therapy. No adverse events were recorded in the willowbark group (Beer & Wegener 2008).

These findings contrast with earlier studies in which willowbark failed to reduce Western Ontario and McMaster Universities Arthritis Index (WOMAC) pain scores better than a placebo in a trial on 127 outpatients with painful hip or knee osteoarthritis (Biegert et al 2004). Patients were randomised to receive willow bark extract, corresponding to 240 mg of salicin/day, diclofenac 100 mg/day, or a placebo. Treatment with diclofenac produced the strongest pain-reducing effects (WOMAC scores decreased by 47%) compared with willowbark (17% reduction) and the placebo (10% reduction), with the difference between willow bark extract and placebo not statistically significant.

> ***Clinical note — Lack of significant haemotological effects***
>
> It has largely been assumed that willowbark alters platelet aggregation and increases bleeding time, in much the same way as aspirin. Whether this is in fact correct and clinically significant has been investigated by Krivoy et al (2001). The clinical study found that consumption of *Salicis cortex* extract (containing 240 mg salicin per daily dose) only minimally affected platelet aggregation compared to a cardioprotective dose of acetylsalicylate (up to 100 mg/day). The particular preparation studied produced a total serum salicylate concentration bioequivalent to only 50 mg acetylsalicylate.

Rheumatoid arthritis (RA)

Willowbark extract (corresponding to 240 mg salicin/day) failed to significantly reduce pain in people with active RA, according to a small, double-blind, randomised study of 26 volunteers (Biegert et al 2004). The main outcome measure used was each patient's assessment of pain rated on a 100 mm visual analogue scale.

Lower back pain

Two randomised studies have investigated the use of oral white willowbark in people with acute episodes of chronic non-specific low-back pain (Chrubasik 2000, 2001a). According to a 2006 Cochrane systematic review, there is moderate evidence that a daily dose of 240 mg salicin from an extract of *S. alba* reduces pain more than either a placebo or a daily dose of 120 mg of salicin in the short term for individuals with acute episodes of chronic non-specific low-back pain (Gagnier et al 2006).

One randomised, placebo-controlled study involving 210 patients with chronic lower back pain found that 39% of those treated with 240 mg salicin became pain-free after 4 weeks compared with 6% in the placebo group. This response was achieved after 1 week (Chrubasik et al 2000). Similar results were achieved in an open trial conducted over 18 months that compared willowbark extract containing 120 mg of salicin or 240 mg salicin with what the authors term 'conventional treatment' in 451 people with acute exacerbations of lower back pain. Those receiving 240 mg salicin experienced the best results, with 40% becoming pain-free after 4 weeks, compared to 19% in the 120 mg salicin group and 18% in the control group (Chrubasik et al 2001b).

Comparative trial with rofecoxib

No significant differences in pain-relieving effects were found between white willowbark, standardised to provide a daily dose of 240 mg salicin,

and 12.5 mg of the synthetic COX-2 inhibitor rofecoxib according to a randomised trial of individuals with acute episodes of chronic non-specific low-back pain (Chrubasik et al 2001a). With regard to rescue treatments, the percentage of patients requiring NSAIDs, tramadol or both was 10% for the willowbark group and 13% for the rofecoxib group. Approximately 90% of physicians and patients rated either treatment as effective and close to 100% rated either treatment as acceptable.

Given that some pharmaceutical treatments used in the management of pain and inflammatory conditions are costly, such as the newer COX-2 inhibitors, Chrubasik et al (2001b) also compared the cost savings associated with the use of willowbark. A dose of 120 mg salicin/day from willowbark reduced overall patient spending on additional drugs by about 35–50%. In comparison, 240 mg salicin/day produced superior pain relief that resulted in even less reliance on supplementary treatments, but savings were outweighed by the extra cost of the higher dose.

In 2007 a systematic review of the same studies, Gagnier et al concluded there is moderate-level evidence to support the acute and short-term use of willowbark for pain at daily doses standardised to 120 mg or 240 mg salicin, where it has relative equivalence to 12.5 mg per day of rofecoxib (Gagnier et al 2007).

Fever and headaches

The known activity of salicylate constituents in the herb provide support for its use as symptomatic treatment in fever and headaches. Commission E has approved willowbark for these indications (Blumenthal et al 2000). Despite this, only one clinical study has been conducted exploring the effectiveness of willowbark for headaches, but it was used in combination with the herb feverfew, so the efficacy of stand-alone treatment remains unknown (Shrivastava et al 2006).

In combination

A prospective, open-label study was performed in 12 patients diagnosed with migraine without aura. Twelve weeks' treatment with feverfew *(Tanacetum parthenium*, 300 mg) plus willowbark (300 mg) twice daily was shown to reduce attack frequency and intensity, with 70% patients having a reduction of at least 50%. Attack duration also decreased significantly in all patients. Self-assessed general health, physical performance, memory and anxiety also improved by the end of the study. The treatment was well tolerated and no adverse events occurred (Shrivastava et al 2006).

OTHER USES

A recent in vitro study that examined the effects of the main groups of compounds (salicylalcohol derivates, flavonoids, proanthocyanidins) and salicin isolated from willowbark extract BNO 1455 found that all compounds exerted antiproliferative activity, inhibited the cell growth and promoted apoptosis in human colon and lung cancer cell lines, irrespective of their COX-selectivity (Hostanska et al 2007)

DOSAGE RANGE

- Tincture (1:1): 1–2 mL three times daily.
- Decoction: 1–3 g finely chopped herb in 1 cup of cold water, brought to the boil then reduced to simmer for 5 minutes, drunk 3–4 times daily.

According to clinical studies

- Osteoarthritic joint pain and inflammation — willowbark preparations standardised to total salicin content and providing 240 mg daily in divided doses.
- Acute episodes of chronic non-specific low-back pain — willowbark preparations standardised to total salicin content and providing 240 mg daily in divided doses.

ADVERSE REACTIONS

None reported. Theoretically, the tannin and salicylate content may cause gastrointestinal disturbances.

SIGNIFICANT INTERACTIONS

Controlled studies are not available, therefore interactions are based on evidence of pharmacological activity and clinical significance is uncertain.

Anticoagulants

Although a clinical study found that consumption of salicin 240 mg/day produced minimal effects on platelet aggregation, higher doses may have a significant effect. Exercise caution with high doses > 240 mg salicin/day.

Salicylate drugs

Theoretically, concurrent use may result in additive effects, although this has yet to be tested. Observe patients taking this combination.

Aspirin

Theoretically, willowbark may enhance the anti-inflammatory and antiplatelet effects at doses of salicin 240 mg/day. Observe patients taking this combination; beneficial interaction may be possible.

An increased risk of bleeding is theoretically possible with high doses > 240 mg salicin. Observe.

NSAIDs

A reduction in drug requirements may be possible with the use of white willowbark for lower back pain according to a randomised study. Beneficial interaction is possible.

CONTRAINDICATIONS AND PRECAUTIONS

Commission E states that there is no evidence that willowbark preparations should be contraindicated in small children because of the risk of Reye's syndrome, as the salicylates in the herb are metabolised differently from those in aspirin.

Owing to the relatively high concentration of salicylates in this herb, it should not be used by people with salicylate sensitivity.

PREGNANCY USE

It is generally not advised to recommend salicylate-containing medicines during pregnancy or lactation, although no restrictions are known for willowbark directly.

PRACTICE POINTS/PATIENT COUNSELLING

- Evidence from several RCTs suggests that willowbark is an effective treatment for relieving pain in chronic backache and osteoarthritis.
- The results of one clinical study suggest it is as effective as 12.5 mg of the synthetic COX-2 inhibitor rofecoxib when used at a daily dose of 240 mg salicin.
- People using willowbark may find they have lowered requirements for traditional anti-inflammatory medicines such as NSAIDs.
- Currently, there is no evidence to suggest gastrointestinal side effects or significant platelet inhibition.
- Due to its salicylate content, people with salicylate sensitivity should avoid use of willowbark.

PATIENTS' FAQs

What will this herb do for me?

Scientific studies have found that willowbark is a useful treatment for relieving pain in osteoarthritis and chronic backache. It may also relieve symptoms of headache and fever.

When will it start to work?

Studies using willowbark preparations in diseases characterised by joint pain have found that effects start within 1 week of use.

Are there any safety issues?

Willowbark appears to be free of major side effects or drug interactions, but it should not be taken by people with salicylate sensitivity.

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Withania

HISTORICAL NOTE The name ashwagandha (one of the common names for this herb) comes from the sanskrit meaning 'horse-like smell'. Apparently, this name not only refers to the smell of the herb but also to its strengthening and aphrodisiac qualities. It is often referred to as 'Indian ginseng' because it is used in much the same way as *Panax ginseng* in TCM, although it is considered less stimulating. In Ayurvedic medicine it is classified as a 'rasayana', used to promote physical and mental health and improve vitality and longevity (Kulkarni & Dhir 2008).

OTHER NAMES

Ashwagandha (and a variety of spellings including ashvagandha, ashwaganda, asvagandha), Ayurvedic ginseng, Indian ginseng, winter cherry

BOTANICAL NAME/FAMILY

Withania somnifera (family Solanaceae)

Sometimes confused with *Physalis alkekengi*, also known as winter cherry.

PLANT PARTS USED

Primarily root, although berry, leaves and bark are sometimes used.

CHEMICAL COMPONENTS

Steroidal lactones (withanolides, withaferin A), alkaloids (including withanine, somniferine, isopelletierine, anaferine, tropine, pseudotropine), flavonoids, saponins, sitoindosides, iron, choline, acylsteryl glucosides, coumarins (scopoletin and aesculetin), triterpene (beta-amyrin), phytosterols (stigmasterol, stigmasterol glucoside, beta-sitosterol and beta-sitosterol glucoside), Viscosa lactone B, alpha+beta glucose, essential oils (ipuranol, withaniol) (Misra et al 2008, Abou-Douh 2002, Kulkarni & Verma 1993, Mills & Bone 2000).

Plants sourced from Sardinia, Italy have significantly higher levels of withaferin A content than those sourced from India or Sicily (Scartezzini et al 2007).

MAIN ACTIONS

Withania and several of its key constituents have been subjected to scientific investigation in vitro and in vivo. Whilst the pharmacological actions of individual components is important to understand, clinical effects are difficult to predict from these studies as the ultimate effect of the herbal treatment will be a result of many intraherbal interactions.

Adaptogen (modulates stress responses)

Withania has been shown to attenuate the negative effects of chronic stress in rats, including hyperglycaemia, glucose intolerance, increase in plasma corticosteroid levels, gastric ulcerations, male sexual dysfunction, cognitive deficits, immunosuppression and mental depression (Bhattacharya & Muruganandam 2003).

Animal trials have shown that a withanolide-free hydrosoluble fraction of withania reduces the stress response induced both chemically and physically (Singh et al 2003). It suppresses stress-induced increases in dopamine receptors in the corpus striatum and acts as a GABA-mimetic agent by binding to GABA receptors (Mehta et al 1991, Upton 2000). Animal studies also suggest an ability to reduce adrenal weight and plasma cortisol levels (Kurandikar et al 1986), thus potentially protecting against the negative effects of elevated cortisol levels in chronic stress and allostasis.

Nervous system activity

Cognitive enhancement

The potent acetylcholinesterase inhibitory activity of withania in vitro may help to explain its traditional use for improving cognition (Vinutha et al 2007). Memory enhancement has been confirmed by animal studies and appears to be mediated by a cholinergic effect (Dhuley 2001). Increased cortical muscarinic acetylcholine receptor capacity has been observed in animals and humans with extracts of withania (Schliebs et al 1997). Several withanolides exert calcium antagonistic ability, together with anticholinesterase activity, by inhibiting butyrylcholinesterase and acetylcholinesterase enzymes (Choudhary MI et al 2004, 2005). The presence of choline in the herb may also contribute to the production of acetylcholine and further increase cholinergic effects.

Neuroprotective

Several animal studies indicate the potential for protection of neurons (Jain et al 2001), including protection from neuronal injury in Parkinson's disease (Ahmad et al 2005) and promotion of dendrite formation (Tohda et al 2000). One possible explanation is due to the antioxidant properties of withania (Parihar & Hemnani 2003).

In animal experiments withania has been shown to be useful for the treatment of drug-induced dyskinesia (chewing movements, tongue protrusion and buccal tremors) due to reserpine (an antihypertensive and antipsychotic agent no longer available in Australia) and haloperidol (an antipsychotic). In one study, *W. somnifera* root extract (50 and 100 mg/kg) was administered for 4 weeks and dose-dependently reduced reserpine-induced vacuous chewing movements and tongue protrusions, and memory retention deficits in rats. The effect was most likely due to reversal of the drug-induced depletion of glutathione (GSH), superoxide dismutase (SOD) and catalase (Naidu et al 2006). Other researchers support the theory that benefits of withania appear to be due to its antioxidant rather than GABA-mimetic action (Bhattacharya SK et al 2002, Naidu et al 2003).

In vitro results suggest that withanolide A, withanoside IV and withanoside VI are involved in reconstructing neuronal networks, including axons, dendrites, pre- and postsynapses in the neurons (Tohda 2008, Kuboyama et al 2002, 2005). In vivo, oral withanolide A, withanoside IV and withanoside VI (10 μmol/kg/day for 12 days) have been shown to improve experimentally-induced memory impairment, neurite atrophy and synaptic loss in the cerebral cortex and hippocampus in mice; and withanoside IV (10 μmol/kg/day for 21 days) improves locomotor functions in mice with spinal cord injury (SCI) (Tohda 2008).

Antioxidant

Withania exerts an indirect antioxidant action in vivo (Bhattacharya SK et al 1997, Bhattacharya A et al 2001). Daily administration of *W. somnifera* root extract increases hepatic glucose-6-phosphatase activity and decreases hepatic lipid peroxidation, most likely by increasing the activity of endogenous antioxidant enzymes (Panda & Kar 1997, 1998, 1999). In vitro *W. somnifera* inhibits both the lipid peroxidation and the protein oxidative modification induced by copper (Gupta et al 2003). In animal studies the antioxidant actions have been proposed as a possible mechanism for withania, preventing the negative effects of stroke induced by middle cerebral artery occlusion in rats (Choudhary G et al 2003). The antioxidant properties may also contribute to the anticataleptic effect noted in studies of haloperidol-induced catalepsy in albino mice (Nair et al 2008).

Increases haematopoiesis

Animal trials indicate the herb increases haemoglobin and red blood cell levels (Ziauddin et al 1996) and increases haematopoiesis (Aphale et al 1998). The iron content of the herb may further contribute to its role in red blood cell formation.

Immunomodulation

Immunomodulating activity has been demonstrated in vivo for withania, including an increase in white blood cell, platelet and neutrophil counts (Agarwal et al 1999, Davis & Kuttan 2000, Gupta YK et al 2001, Ziauddin et al 1996), proliferation of lymphocytes, increased INF-gamma (Teixeira et al 2006) and IL-2 levels and a reduction in TNF (Davis & Kuttan 1999). In vitro, increased nitric

oxide production by macrophages has also been reported (Iuvone et al 2003). Withaferin A and withanolide D may cause immunosuppression, but other factors have immunostimulant effects (NMCD 2005).

In animal studies, oral administration of a standardised fluid extract (1:1) of withania (30 mg/kg) for 15 days resulted in enhanced Th1 immunity (increased expression of T helper cell (Th1) cytokines, interferon (IFN)-gamma and interleukin (IL)-2) with a moderate decline in Th2 (decreased expression of Th2 cytokine IL-4). This effect appeared to be due to withanolide A. The extract also strongly activated macrophage function and no toxicity was noted (Malik et al 2007). Other studies have confirmed an increased expression of Th1 cytokines in chronically stressed (Khan et al 2006) and immunosuppressed mice (Bani et al 2006). Although human trials are required to confirm these effects, withania shows promise for selective Th1/Th2 modulation.

Antibacterial and antifungal activity

Animal and in vitro studies have shown antibacterial effects against *Staphylococcus aureus*, *Listeria monocytogenes*, *Bacillus anthracis*, *Bacillus subtilis*, *Salmonella enteridis* (Akin et al 1986) and *Salmonella typhimurium* (Owais et al 2005). The methanol and hexane extracts of both the leaves and the roots have potent antibacterial activity against *S. typhimurium* and *Escherichia coli* (Arora et al 2004); and the steroidal withanolides from the related species *W. coagulens* have been found to have antifungal activity against *Allescheria boydii*, *Aspergillus niger*, *Curvularia lunata*, *Drechslera rostrata*, *Epidermophyton floccosum*, *Microsporum canis*, *Nigrospora oryzae*, *Pleurotus ostreatus* and *Stachybotrys atra* (Choudhary et al 1995). *W. somnifera* glycoprotein exerts an antibacterial activity against *Clavibacter michiganensis* and a fungistastic effect against *Aspergillus flavus, Fusarium oxysporum* and *F. verticilloides* (by inhibiting spore germination and hyphal growth) (Girish et al 2006).

Anti-inflammatory activity

Withania extract suppresses the production of pro-inflammatory molecules in vitro. This is partly due to inhibition of transcription factors NF-kappaB and AP-1 by withanolides (steroidal lactones) (Ichikawa et al 2006, Kaileh et al 2007, Singh et al 2007). Several withanolides exert selective COX-2 enzyme inhibition (Jayaprakasam & Nair 2003) and withania has been found to decrease alpha-2-macroglobulin, a liver-synthesised plasma protein that increases during inflammation (Anbalagan & Sadique 1985). A reduction in the erythrocyte sedimentation rate has also been noted in a double-blind clinical trial of 50–59 year old males (Kupparajan et al 1980).

Chondroprotective

Withania root powder has demonstrated chondroprotective effects in vitro (human osteoarthritic cartilage matrix) inhibiting the gelatinase activity of collagenase type 2 enzyme and exerting a significant short-term chondroprotective effect in a subset (50%) of patient samples (Sumantran et al 2007). In vivo the root powder rectified biochemical changes resulting from experimentally-induced arthritis in rats (Rasool & Varalakshmi 2007). Associated with arthritis were increased levels of lipid peroxides, glycoproteins and urinary constituents; and depletion of antioxidant status and bone collagen. These biochemical alterations were ameliorated significantly by oral administration of *W. somnifera* root powder (1000 mg/kg body weight) in test animals. It should be noted however that the high dose used (1000 mg/kg bodyweight) is not likely to be reproducible in human trials.

Anticancer (antineoplastic and chemoprevention)

In vitro studies have determined that withania extracts possess cell-cycle disruption and anti-angiogenic activity (Mathur et al 2006). Withania stimulates the production of cytotoxic T-lymphocytes in vivo and in vitro, and may prevent or reduce tumour growth (Davis & Kuttan 2002, Jayaprakasam et al 2003). In animal models, withania was found to prevent skin carcinoma induced by UVB radiation (Mathur et al 2004) and forestomach tumours (Padmavathi et al 2005); reduce the incidence, number and size of tumours; and to counteract the associated decrease in body weight (Singh et al 1986).

The withaferin A fraction appears to exert anti-angiogenic activity (Mohan et al 2004), antigenotoxic effects on bone marrow (Panjamurthy et al 2008), and may be partly responsible for the antineoplastic effects observed in both in vitro and in vivo studies (Uma Devi 1995, 1996). The antioxidant effects aid in the prevention of DNA damage by mutagens (Khanam & Devi 2005) and this in combination with detoxifying properties, anti-inflammatory and immunomodulatory effects, determined in animal studies, are likely to contribute to its chemopreventive action (Prakash et al 2001, 2002).

Because several genes that regulate cellular proliferation, carcinogenesis, metastasis and inflammation are regulated by nuclear factor-kappaB (NF-kappaB), the ability of withanolides to inhibit activation of NF-kappaB and NF-kappaB-regulated gene expression may partly explain the role of withania in enhancing apoptosis and inhibiting invasion and osteoclastogenesis (Ichikawa et al 2006).

Anxiolytic and antidepressant

Animal studies have found glycowithanolides exert anxiolytic effects comparable to those of lorazepam, and antidepressant effects comparable to those of the antidepressant drug imipramine (Bhattacharya SK et al 2000).

Anxiolytic and antidepressant activities have also been demonstrated for the withania root extract (WS 100, 200 or 500 mg/kg) and potentiation of diazepam at sub-therapeutic doses (WS 50 mg/kg) have been demonstrated (Gupta and Rana 2007).

OTHER ACTIONS

Blood glucose control

Withania extract (200 and 400 mg/kg) was administered orally once daily for 5 weeks in a type 2 diabetes experimental model. The treatment reduced elevated levels of blood glucose, HbA_{1c} and insulin, and improved glucose tolerance and insulin sensitivity (Anwer et al 2008). In experimental in vitro models, withania (especially the ethanolic extract) has shown effects comparable to metformin in preventing the formation of advanced glycation end products (AGE), which are implicated in the pathogenesis of diabetes mellitus (Babu et al 2007).

Cardioprotective

Cardioprotective effects have been noted in animal studies (Dhuley 2000, Mohanty et al 2004), significantly reducing myocardial injury after ischaemia and reperfusion (Gupta et al 2004). These effects are most likely due to restoration of the myocardial oxidant–antioxidant balance and the marked anti-apoptotic properties of withania (Mohanty et al 2008). Cardioprotective effects were also observed against doxorubicin-induced cardiotoxicity in vivo when pretreatment with a standardised withania extract (300 mg/kg; 1.5% withanolides) was administered before drug exposure (doxorubicin 10 mg/kg) (Hamza et al 2008). The alkaloids are considered to be sedative and reduce blood pressure and heart rate (Chevallier 1996, Malhotra et al 1965a). The withanolides have a chemical structure similar to cardiac glycosides and have demonstrated mild ionotropic and chronotropic effects on the heart (Roja et al 1991, Tripathi et al 1996).

Antihypercholesterolaemic

High doses of withania root powder (0.75 and 1.5 g/day) produced significant decreases in total lipids (–40.54%; –50.69%), cholesterol (–41.58%; –53.01%) and triglycerides (–31.25%; –44.85%); and significant increases in HDL-cholesterol levels (+15.10%; +17.71%) in an experimental model of hypercholesterolaemia. Additionally, treatment resulted in significant decreases in HMG-CoA reductase activity and bile acid content in the liver of these animals, and there was a trend towards increased excretion of bile acid (+22.43%;+28.52%), cholesterol (+14.21%; +17.68%) and neutral sterol (+12.40%; +18.85%). Lipid-peroxidation also decreased significantly (–35.29%; –36.52%) (Visavadiya & Narasimhacharya 2007). The doses used in this study may not be feasible in humans.

Thyroid modulating

An in vivo study reported that daily administration of *W. somnifera* root extract enhanced serum T_4 concentration (Panda & Kar 1998, 1999). However, there is one case report of thyrotoxicosis in a 32-year-old woman attributed to a withania-containing herbal capsule (van der Hooft et al 2005), so caution is advised.

Sexual enhancer

Traditionally used for this purpose, one double-blind clinical trial found that a dose of 3 g taken daily for 1 year improved the sexual performance of 71.4% of healthy ageing males (Kupparajan et al 1980). Alternatively, animal studies have indicated that very high doses (3000 mg/kg) result in reduced sexual performance (Ilayperuma et al 2002).

Hepatoprotective

Animal studies have demonstrated hepatoprotective effects (Bhattacharya A et al 2000, Sudhir et al 1986) and that withania inhibits phase I, and activates phase II and antioxidant enzymes in the liver (Padmavathi et al 2005).

Anticonvulsant

Withania root extract (100 or 200 mg/kg orally) increases seizure threshold in mice. The effect is likely due to GABA-A modulation (Kulkarni et al 2008).

CLINICAL USE

Overall, *W. somnifera* has not undergone significant scientific investigation in humans, therefore much of its use is based on pharmacological effects demonstrated in experimental models or traditional usage. In practice, it is often used in herbal combination treatments.

Stress adaptation

The pharmacological effects of the herb, which have been well established in animal studies, provide a theoretical basis for its use in situations characterised by stress (Archana & Namasivayam 1999, Bhattacharya & Muruganandam 2003, Dhuley 2000, Grandhi et al 1994).

More specifically, oral administration of an aqueous, standardised extract of *W. somnifera* (in a dose extrapolated from the human dose) has been found to offer protection against experimentally induced biological, physical and chemical stressors (Rege et al 1999).

In one in-vivo study, plasma cortisol levels and adrenal weight were significantly lower, while liver weight increased (Kurandikar et al 1986).

To date, controlled studies are unavailable to determine and clarify whether these effects are also significant in humans.

(For more information see 'Clinical note — Allostasis and adaptation to stress' in the Siberian ginseng monograph.)

Anxiety

Although double-blind human studies are lacking, the herb's pharmacological effects, such as its GABA-mimetic activity (Mehta et al 1991) and ability to lower cortisol levels (Kurandikar et al 1986), provide a theoretical basis for its use in anxiety states. In vivo studies with withania root extract (WS 100, 200 or 500 mg/kg) confirm its anxiolytic effects and its ability to potentiate diazepam at subtherapeutic doses (WS 50 mg/kg) (Gupta & Rana 2007).

One study used a herbal combination treatment known as Geriforte, which contains primarily *W. somnifera*. The product was taken by 34 subjects with anxiety neurosis, and after 12 weeks significant reductions in the frequency, duration and intensity of symptoms were observed (Ghosal et al 1990).

Anabolic and weight gain promotion

Both animal and human studies have shown significant improvements in weight gain during the growth phase with the use of withania (Sharma et al 1986, Ziauddin et al 1996). It is suspected that an anabolic effect is responsible.

Withania-fortified milk (2 g/day for 60 days) has been investigated in children and found to induce weight gain, increase total plasma proteins and haemoglobin levels (Venkatraghaven et al 1980).

Anaemia

The herb is used in the treatment of iron deficiency anaemia due to its effects on haemopoeisis and natural iron content (Aphale et al 1998, Ziauddin et al 1996). This use has been supported by studies showing increased haemoglobin levels in children, induced by withania.

Cancer therapy

W. somnifera appears to reduce tumour cell proliferation while increasing overall survival time in animal trials. It enhances the effectiveness of radiation therapy while potentially attenuating the undesirable side effects of radio- and chemotherapeutic agents (including cyclophosphamide and paclitaxel) without interfering with the tumour-reducing actions of the drugs (Winters 2006).

Withania has been attributed with anti-tumour activity (Davis & Kuttan 2002, Jayaprakasam et al 2003), anti-angiogenic effects (Mathur et al 2006, Mohan et al 2004) as well as antigenotoxic effects on bone marrow (Panjamurthy et al 2008). The antioxidant effects aid in the prevention of DNA damage by mutagens (Khanam & Devi 2005) and this in combination with detoxifying properties, anti-inflammatory and immunomodulatory effects, determined in animal studies, are likely to contribute to its chemopreventive action (Prakash et al 2001, 2002).

Animal studies suggest a potential role for withania as an adjunctive treatment during chemotherapy for the prevention of drug-induced bone marrow depression (Davis & Kuttan 1999, Gupta et al 2001).

The ability to stimulate stem-cell proliferation has led to concerns that *W. somnifera* could reduce cyclophosphamide-induced toxicity and therefore reduce its usefulness in cancer therapy (Davis & Kuttan 1998). However, preliminary animal studies indicate that withania could prove to be a potent and relatively safe radiosensitiser and chemotherapeutic agent (Uma Devi 1996). In one animal experiment, pretreatment with a standardised withania extract (300 mg/kg; 1.5% withanolides) attenuated the cardiotoxic side-effects of doxorubicin (10 mg/kg) (Hamza et al 2008). In mice, the addition of *W. somnifera* (400 mg/kg orally once weekly for 4 weeks) to paclitaxel treatment (33 mg/kg intraperitoneally once weekly for 4 weeks) may extend its chemotherapeutic effect through modulating protein-bound carbohydrate levels and marker enzymes. The combination may effectively treat benzo(a)pyrene-induced lung cancer by offering protection against damage from reactive oxygen species and also by suppressing cell proliferation (Senthilnathan et al 2006a).

Drug withdrawal

In animal studies, repeated administration of withania (100 mg/kg) inhibited morphine tolerance and dependence (Kulkarni & Ninan 1997). Based on this observation, and its ability to modulate stress responses in general, withania is used in herbal combination therapy during opiate withdrawal. It may also be useful in the management of withdrawal-induced anxiety due to chronic ethanol consumption (Gupta & Rana 2008).

Arthritis

The documented anti-inflammatory, chondroprotective (Rasool & Varalakshmi 2007, Sumantran et al 2007) and antioxidant activities of withania provide some support for its traditional use in arthritis. Arthritis results from dysregulation of pro-inflammatory cytokines (e.g. TNF and IL-1 beta) and enzymes that mediate the production of prostaglandins (e.g. cyclooxygenase-2) and leukotrienes (e.g. lipooxygenase), together with the expression of adhesion molecules and matrix metalloproteinases, and hyperproliferation of synovial fibroblasts. These factors are regulated by the activation of the transcription factor nuclear factor-kappaB, which is inhibited by withanolides (Khanna et al 2007).

Withania root powder (500 and 1000 mg/kg) exerts a potent analgesic effect in rats and appears to retard amplification and propagation of the inflammatory response without causing any gastric damage (Rasool & Varalakshmi 2006).The root powder (1000 mg/kg) has also been shown to rectify biochemical changes resulting from experimentally-induced arthritis (Rasool & Varalakshmi 2007). It should be noted however that this dose is not likely to be reproducible in human trials.

Osteoporosis

An ethanolic extract of withania root markedly prevented bone loss and associated biochemical changes in ovariectomised rats indicating possible prevention of osteoporosis (Nagareddy & Lakshmana 2006). Controlled trials in humans are currently lacking.

Sleep

As its alkaloids are considered to be sedative and able to reduce blood pressure and heart rate (Chevallier 1996, Malhotra et al 1965a), withania is also used as a treatment for insomnia, although controlled trials are lacking in this area. Compared to diazepam (0.5 mg/kg) alone, the addition of withania root extract (100 mg/kg) to sleep disturbed mice significantly attenuates the negative consequences of sleep deprivation. These include; reduction in body weight,

reduced locomotor activity, anxiety and altered antioxidant status (Kumar & Kalonia 2007).

OTHER USES

Traditionally used in convalescence for people who are stressed and both physically and emotionally exhausted. It is considered a non-stimulating tonic allowing for the restoration of vitality.

In rural parts of India, withania is applied topically as an antidote to snakebite. *W. somnifera* glycoprotein inhibits the hyaluronidase activity of cobra (*Naja naja*) and viper (*Daboia russelii*) venoms providing some support for this use (Machiah et al 2006). Hyaluronidase activity is involved in rapid spreading of the toxins by destroying the integrity of the extra-cellular matrix.

DOSAGE RANGE

- Fluid extract (1:1): 20–50 mL/week (Australian manufacturer recommendations).
- Dried root: 3–6 g/day in capsule or tea form.

ADVERSE REACTIONS

Large doses can cause gastrointestinal upset, diarrhoea and vomiting (Tierra 2005).

A case report exists of thyrotoxicosis in a 32-year-old woman after taking a herbal capsule containing withania (van der Hooft et al 2005). Central nervous system and respiratory depression (Malhotra et al 1965b), decreased body temperature (Malhotra et al 1965b), gastrointestinal upset (Lindner 1996) and kidney and liver abnormalities (Arseculeratne et al 1985) have also been noted.

Acute toxicity studies in animals show a good margin of safety with a high therapeutic index (Aphale et al 1998, Rege et al 1999, Sharada et al 1993, Singh et al 2001, 2003).

SIGNIFICANT INTERACTIONS

Controlled studies are not available; therefore, interactions are based on evidence of activity and are largely theoretical and speculative.

Antipsychotic/neuroleptic agents

In animal experiments, withania has been shown to be useful in the treatment of drug-induced dyskinesia (chewing movements, tongue protrusion and buccal tremors) due to reserpine and haloperidol (Bhattacharya SK et al 2002, Naidu et al 2003, 2006). Beneficial interaction possible.

Barbiturates

Additive effects are theoretically possible leading to increased sedation (NMCD 2005, Tierra 2005). Observe patients taking withania and barbiturates concurrently — beneficial interaction possible under medical supervision.

Benzodiazepines

Based on evidence from in vivo models (Kumar & Kalonia 2007), an increased sedative effect is theoretically possible (Upton 2000). Observe patients taking withania and benzodiazepines concurrently. Beneficial interaction possible under professional supervision.

Chemotherapy

Animal studies suggest a potential role for withania as an adjunctive treatment during chemotherapy. Observe — beneficial interaction may be possible — only to be used under professional supervision.

Cyclophosphamide

While the ability to stimulate stem-cell proliferation has led to concerns that *W. somnifera* could reduce cyclophosphamide-induced toxicity and therefore reduce its usefulness in cancer therapy (Davis & Kuttan 1998), preliminary animal studies indicate that withania could prove to be a potent and relatively safe radiosensitiser and chemotherapeutic agent (Uma Devi 1996).

Doxorubicin

In rats pretreatment with a standardised withania extract (300 mg/kg; 1.5% withanolides) attenuates the cardiotoxic side-effects of doxorubicin (10 mg/kg) (Hamza et al 2008).

Paclitaxel

In mice the addition of *W. somnifera* (400 mg/kg, orally once weekly for 4 weeks) to paclitaxel (33 mg/kg, intraperitoneally once weekly for 4 weeks) may extend its chemotherapeutic effect through modulating protein-bound carbohydrate levels and marker enzymes. The combination may effectively treat the benzo(a)pyrene-induced lung cancer by offering protection from oxidative damage and also by suppressing cell proliferation (Senthilnathan et al 2006a, b).

Digoxin assays

Withania may modestly interfere with serum digoxin measurements by the fluorescent polarisation immunoassay (FPIA) and other assays (Dasgupta et al 2007, 2008).

Immunosuppressants

The ability to stimulate stem-cell proliferation has led to concerns that *W. somnifera* could reduce the effectiveness of immunosuppressant drugs (Davis & Kuttan 1998). Caution should be exercised with patients taking immunosuppressants concurrently; however, a beneficial interaction may be possible under professional supervision.

Morphine

In animal studies, repeated administration of withania (100 mg/kg) inhibited morphine tolerance and dependence (Kulkarni & Ninan 1997). For this reason it is sometimes used in opiate withdrawal. Beneficial interaction possible under professional supervision.

Thyroid medication (e.g. levothyroxine)

Additive effects are theoretically possible. An in vivo study reported that daily administration of withania enhanced serum T4 concentrations (Upton 2000) and a case report exists of withania-induced thyrotoxicosis (van der Hooft et al 2005) — observe patients taking withania and thyroid medications concurrently.

PRACTICE POINTS/PATIENT COUNSELLING

- Withania is an Ayurvedic herbal medicine also referred to as Indian ginseng or ashwaganda. Overall, it has not undergone significant scientific investigation in humans and therefore much of its use is based on pharmacological effects demonstrated in experimental models or traditional usage. It is traditionally used for improving stress adaptation responses in people who are both physically and emotionally stressed and exhausted, and during periods of convalescence.
- Preliminary evidence suggests it increases haematopoiesis, promotes weight gain, reduces anxiety symptoms, increases cognitive function and exerts a neuroprotective effect.
- It has also demonstrated antioxidant, immunomodulating, antineoplastic, antifungal and antibacterial activity in animal or test tube studies.
- The herb should not be taken in pregnancy, and used with caution in people sensitive to the Solanaceae family of plants.

CONTRAINDICATIONS AND PRECAUTIONS

Use with caution in peptic ulcer disease: withania may cause gastrointestinal irritation (Upton 2000). People who are sensitive to the Solanaceae family should use this herb with caution.

PREGNANCY USE

Contraindicated in pregnancy (Lindner 1996) due to a reputed abortifacient activity and antifertility effects noted in animal studies, despite there being no evidence of fetal damage (Mills & Bone 2005).

PATIENTS' FAQs

What will this herb do for me?

Withania has not undergone much scientific investigation in humans, so it is difficult to predict what effects will occur using this source of information. However, according to traditional usage and other studies, it may improve stress responses, reduce symptoms of anxiety, improve memory and mood, increase red blood cell production, increase immune responses and promote weight gain and is useful in convalescence.

When will it start to work?

Symptoms of anxiety and stress improve within 3 months' continual use. It is not known when other effects start to develop.

Are there any safety issues?

The herb should not be taken in pregnancy, and used with caution in people sensitive to the Solanaceae family of plants.

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Zinc

BACKGROUND AND RELEVANT PHARMACOKINETICS

Zinc is an essential trace element known to play an important role in all human living cells. The human body contains approximately 2 g zinc in total, distributed across all body tissues and fluids, with 60% found in skeletal muscle and 30% in bone mass (Wahlqvist et al 2002). Its wide distribution and diverse roles have attracted the label as the 'ubiquitous nutrient' given by some authors (Hambidge 2000, King & Cousins 2006). Zinc belongs to the class of type II nutrients which are considered the cellular building blocks (Golden 1996, King & Cousins 2006) and therefore zinc, together with

the other type II nutrients (essential amino acids, magnesium, potassium, phosphorus, protein and sulfur) is required for the synthesis of any new tissue. They are not stored by the body and are under tight physiological control.

Dietary intake of zinc by healthy adults is 6–15 mg/day, however, less than half of this is absorbed (Beers & Berkow 2003). Zinc absorption is now recognised as being influenced by many factors and adequate dietary intake does not guarantee adequate zinc status. The International Zinc Nutrition Consultative Group (IZiNCG) concludes that the two key modulators of zinc bioavailability from any given diet are phytates and calcium. Foods with high phytate content significantly reduce zinc absorption due to the formation of strong and insoluble complexes (Lonnerdal 2000) and a phytate:zinc molar ratio ≥ 15, e.g. whole grains, seeds and nuts, is reported to render the zinc virtually unobtainable (IZiNCG 2004). In addition to this, calcium in large amounts constitutes the main antagonistic mineral interaction and therefore, calcium-rich diets may also precipitate zinc deficiency. Alternatively, the amount of animal protein in a meal positively correlates to zinc absorption and the amino acids histidine and methionine, and various organic acids present in foods, such as citric, malic and lactic acids, can also increase absorption. As such, zinc, similarly to iron, is best absorbed from animal food sources (King 2003).

CHEMICAL COMPONENTS

Zinc sulfate and gluconate are the most commonly used forms in supplements.

FOOD SOURCES

Meat, liver, eggs and seafood (especially oysters and shellfish) are the best sources. While zinc is also found in nuts, legumes, whole grains and seeds, the high phytate content of these foods may render them an inferior source. Phytates can be reduced through fermentation or sprouting, however, which in turn would improve zinc bioavailability in these foods. Other dietary sources include miso, tofu, brewers' yeast, mushrooms and green beans.

DEFICIENCY SIGNS AND SYMPTOMS

Severe deficiency is rarely seen in industrialised countries, but marginal deficiency and inadequate intakes are not uncommon. According to a large national survey of over 29,000 people conducted in the USA, only 55.6% had adequate zinc intakes (based on total intakes of >77% of the 1989 US recommended daily intake (RDI) levels). Young children aged 1–3 years, female adolescents and older people aged ≥71 years had the lowest percentage of 'adequate' zinc intake, and were identified at greatest risk of deficiency (Briefel et al 2000). Others at risk are alcoholics (especially those with liver disease), pregnant and lactating women, teenagers experiencing rapid growth, malnourished individuals including those with anorexia nervosa, people with severe or chronic diarrhoea, malabsorption syndromes or inflammatory bowel diseases, and strict vegetarians.

Zinc repletion facilitates growth and replication of individual cells and the organism at large. Consequently, the frank deficiency picture is characterised by impaired growth (linear growth velocity, weight or body composition) (Hambidge 2000). This will produce overt presentations in those life stages and tissues necessitating rapid replication and turnover for health (Hambidge 2000), e.g. embryos, early childhood, adolescence, immune cells, epidermal and gastrointestinal tissue (Hambidge 2000, IZiNCG 2004, King 2000, King & Cousins 2006, Mahomed et al 1993), but often indiscernible pictures outside of these. The clinical picture of mild zinc deficiency is subtle, ambiguous, idiosyncratic (Golden 1996, Hambidge 2000) and notoriously difficult to diagnose (Golden 1996, Wood 2000). A prominent zinc researcher says, 'the ubiquity and versatility of zinc in subcellular metabolism suggest that zinc deficiency may well result in a generalised impairment of many metabolic functions' (p. 1345S) (Hambidge 2000).

Signs and symptoms of deficiency

Most consistently reported:

- Anorexia, impaired sense of taste and smell.
- Slowed growth and development.
- Delayed sexual maturation, hypogonadism, hypospermia and menstrual problems.
- Dermatitis, particularly around the body's orifices as seen in acrodermatitis enteropathica.
- Alopecia.
- Chronic and severe diarrhoea.
- Immune system deficiencies and increased susceptibility to infection, including bacterial, viral and fungal.
- Impaired wound healing due to decreased collagen synthesis.
- Night blindness; swelling and clouding of the corneas.
- Behavioural disturbances such as mental fatigue and depression (King 2003).

Less consistently reported:

- Erectile dysfunction.
- Anergy.
- Glossitis.
- Nail dystrophy.
- Hypopigmented hair.
- Photophobia.
- Photic injury.
- Swelling and clouding of the corneas.
- Reduced serum testosterone in males.
- Reduced alcohol clearance.
- Hyperammonaemia.
- Impaired protein synthesis.

Zinc deficiency in pregnancy is associated with the following (Bedwal & Bahuguna 1994, Prasad 1996):

- Increased maternal morbidity, pre-eclampsia and toxaemia.
- Prolonged gestation.
- Inefficient labour.
- Atonic bleeding.
- Increased risk of abortion and stillbirths.
- Teratogenicity.

- Low birth weight infants.
- Diminished attention in the newborn and poorer motor function at 6 months (Higdon 2003).

Primary deficiency

This can result from inadequate dietary intake of zinc, for example, strict vegetarians and vegans are at risk of deficiency if their major food staples are grains and legumes, due to their phytate content. Premature and low birth weight infants, pregnant women, adolescents and the elderly are also at risk of inadequate intake, often in the face of increased demands (Briefel et al 2000).

Secondary deficiency

Impaired zinc absorption is also a common cause of zinc deficiency (Lonnerdal 2000), for example in some people with cirrhosis and malabsorption syndromes. Other conditions produce increased losses of zinc, e.g. severe burns, major surgery, chronic diarrhoea, diabetes, HIV and AIDS, and during prolonged parenteral nutrition (Prasad et al 1999). Additionally, strenuous exercise and elevated ambient temperatures increase zinc losses through perspiration. A rare congenital disorder known as acrodermatitis enteropathica, which typically manifests 4–6 weeks after weaning, indicates a significantly compromised ability to absorb zinc forms other than that which is present in breast milk. Consequently, prior to diagnosis and life-long supplementation, infants or children suffering this condition rapidly develop signs of severe zinc deficiency which include the key features listed above, e.g. dermatitis, growth retardation, diarrhoea and alopecia.

MAIN ACTIONS

Important co-factor in many biochemical reactions

In humans, zinc metalloenzymes outnumber all the other trace mineral-dependent enzymes combined, with between 70 and 200 present in humans (Gropper et al 2009), found across all six different enzyme classes (Hambidge 2000). Consequently,

Clinical note — Measuring zinc status is difficult

According to the scientific evidence, there is currently no means of assessing zinc status in humans (particularly with respect to the detection of marginal deficiency states) that has demonstrated absolute accuracy, and the identification of such a test has been flagged as an area requiring urgent research (Bales et al 1990, Hambidge 2000, IZiNCG 2004, Wood 2000). The assessment of zinc in orthodox medicine currently utilises serum or plasma assays (Gropper et al 2009, IZiNCG 2004, Wood 2000). Principally validated as a tool to assess zinc adequacy of populations (IZiNCG 2004, Wood 2000), serum/plasma zinc lacks the sensitivity to accurately ascertain the zinc status of the individual, with decreased values reflective of end-stage depletion only (Gordon et al 1982, Gropper et al 2009, Hambidge 2000, 2003, IZiNCG 2004, Wood 2000). Multiple established confounding variables include diurnal variation, concomitant infections and inflammation, acute stress and trauma, haemodilution of pregnancy, low-serum albumin, high white blood cell counts and the concomitant use of hormones and steroids (King & Cousins 2006, Wood 2000). Each of these scenarios is susceptible to producing false negatives, underpinning concerns regarding the specificity of serum/plasma zinc assessment (Hambidge 2003, Hotz et al 2003). In addition to this, data from the National Health and Nutrition Examination Survey (NHANES II) revealed significant differences in the mean values of 'healthy individuals' dependent on age and sex alone (IZiNCG 2004). In spite of these documented limitations, this test remains the first line assay in orthodox medicine.

A range of other biochemical indices have been used to assess zinc, including red (Kenney et al 1984, Prasad 1985) and white blood cells (Bunker et al 1987, Prasad 1985), platelets (Baer & King 1984), hair (Bunker et al 1987, Erten et al 1978, Hambidge 2003, McBean et al 1971, McKenzie 1979), nails (McKenzie 1979), saliva (Bales et al 1990, Freeland-Graves et al 1981, Greger & Sickles 1979), sweat (Baer & King 1984, Eaton et al 2004) and urinary concentrations (Hambidge 2003, McKenzie 1979, Prasad 1985). All represent static measures and, as such, lack the sensitivity required to account for zinc's dynamic and complex homeostasis (Gropper et al 2009). Many researchers believe that an accurate indicator of zinc nutriture will therefore also need to be dynamic, similar to using ferritin as a marker for iron status (Hambidge 2000, Hambidge 2003, Wood 2000).

One area of functional zinc assessment extensively researched since the 1970s is taste acuity testing (Gibson 1990, Gibson et al 1989, Henkin et al 1975b,). Hypogeusia is recognised as an early indicator of zinc deficiency (Buzina et al 1980, Gibson 1990, Henkin et al 1975a, Kosman & Henkin 1981, Tanaka 2002, Wright et al 1981) and is believed to be the result of compromised gustin activity, a carbonic anhydrase zinc metalloenzyme, which facilitates differentiation, growth and turnover of taste buds (Gibson et al 1989, Henkin et al 1975b, 1977, Law et al 1987, Thatcher et al 1998). The zinc taste response test (also known as the Bryce-Smith taste test) is a popular measure among naturopathic practitioners. It relies on patients detecting a taste after oral administration of 5–10 mL of a zinc sulfate heptahydrate solution. Delayed taste perception or lack of taste recognition is interpreted as a zinc deficiency state. This method is not particularly accurate and is hampered by variations in patients' subjective sense of taste and the fact that agents other than zinc influence taste perception. Clinical studies with zinc taste tests have confirmed the inconsistency of the results (Birmingham et al 2005, Eaton et al 2004, Garg et al 1993, Mahomed et al 1993).

zinc is involved in myriad chemical reactions that are important for normal body functioning, such as carbohydrate metabolism, protein and DNA synthesis, protein digestion, bone metabolism and endogenous antioxidant systems (Merck 2009, Wahlqvist et al 2002, Wardlaw et al 1997). At the cellular level, zinc's functions can be divided into three categories: catalytic, structural and regulatory (King 2003). Zinc ions perform structural roles in a range of proteins and biomembranes. Of particular note is the zinc finger motif which occurs in transcriptional proteins, directing their binding to DNA and subsequent gene expression. The zinc ion is considered to play the key role in this interaction (Hambidge 2000). Zinc's contribution as an intra- and intercellular regulatory ion continues to emerge and currently includes its influence upon gene expression, receptor-mediated signal transduction, antigen-dependent T-cell activation, insulin-like growth factor receptor binding and glutamatergic activity in the central nervous system (Hambidge 2000, King & Cousins 2006). In its catalytic capacity, zinc metalloenzymes are defined as those apometalloenzymes which are dependent upon the binding of zinc for their activity.

Growth and development

Zinc is important for the formation of biomembranes and zinc finger motifs found in DNA transcription factors (Semrad 1999) and, belonging to the type II nutrient class, is required for the building of all new tissues.

Normal immune responses

Zinc is involved in many aspects of immunological function. It is essential for the normal development and function of cells, for mediating non-specific immunity such as neutrophils and natural killer cells and for affecting development of acquired immunity and T-lymphocyte function. Deficiency primarily impacts on T-lymphocyte function, reducing both peripheral numbers and thymic cells, compromising function of the T helper and cytotoxic cells and reducing serum levels of thymulin. In addition to this, zinc depletion rapidly diminishes antibody and cell-mediated responses in both humans and animals, all together leading to increases in opportunistic infections and mortality rates (Fraker et al 2000). Animal models have shown that suboptimal intake of zinc over 30 days can lead to 30–80% loss in defence capacity. Investigation using a human model has demonstrated that even mild deficiency in humans adversely affects T-cell functions (Prasad 1998). Conversely, high-dose zinc supplementation (20-fold RDI) can also produce immune dysfunction due to an induced copper deficiency. Zinc supplementation also influences cytokine production with reduced tumour necrosis factor (TNF)-alpha and interleukin (IL)-beta in healthy adults (Overbeck et al 2008).

Neurological function

Zinc ions are unevenly distributed in the central nervous system (CNS), acting as neurosecretory products or co-factors. Zinc is highly concentrated in the synaptic vesicles of specific neurons, known as 'zinc-containing' neurons (Frederickson & Danscher 1990, Frederickson & Moncrieff 1994, Frederickson et al 2000). Zinc-containing neurons are a subset of glutamatergic neurons and are mostly located in the telencephalon. Zinc is released from zinc-containing neurons in a calcium- and impulse-dependent manner, producing a broad spectrum of neuromodulatory effects. Additionally, zinc appears to stabilise the storage of certain macromolecules in presynaptic vesicles.

Reproduction

In humans, zinc is necessary for the formation and maturation of spermatozoa, for ovulation and for fertilisation (Favier 1992). Zinc has multiple actions on the metabolism of androgen hormones, oestrogen and progesterone, and these, together with the prostaglandins and nuclear receptors for steroids, are all zinc finger proteins.

In adult males, zinc content is high in the testis and prostate, which have the highest concentration of zinc of any organ in the body (Bedwal & Bahuguna 1994).

In women, zinc deficiency in pregnancy has been associated with increased maternal morbidity, increased risk of abortion, stillbirth, teratogenicity and other unwanted outcomes (Bedwal & Bahuguna 1994).

Antioxidant

Zinc limits oxidant-induced damage in a number of indirect ways, such as by protecting against vitamin E depletion, controlling vitamin A release, contributing to the structure of the antioxidant enzyme extracellular superoxide dismutase, restricting endogenous free radical production, maintaining tissue concentrations of metallothionein, a possible scavenger of free radicals, and stabilising membrane structure (DiSilvestro 2000). It was observed to decrease lipid peroxidation and protect mononuclear cells from TNF-alpha-induced NF-kappa-B activation associated with oxidative stress (Prasad et al 2004).

Insulin-like activity

One of the in vivo features of zinc is its insulin-like function, which is mediated via inhibition of endogenous GSK-3 (Ilouz et al 2002). This is important because GSK-3 inhibition appears essential for normal function of the insulin-activated signalling pathway.

CLINICAL USE

Many of the clinical uses of zinc supplements are for conditions thought to arise from a marginal zinc deficiency, but some indications are based on the concept that high-dose zinc supplements act as a therapeutic agent above and beyond the point of repletion.

Deficiency

Traditionally, zinc supplementation has been used to treat deficiency or prevent deficiency in conditions such as acrodermatitis enteropathica, anorexia

nervosa, malabsorption syndromes, conditions associated with chronic diarrhoea, alcoholism, diabetes, HIV and AIDS, recurrent infections, severe burns, Wilson's disease and sickle cell anaemia. Zinc supplements are also popular among athletes in order to counteract zinc losses that occur through perspiration.

Common cold

Oral zinc supplements, lozenges, nasal sprays and gels have been investigated in the treatment of the common cold. It has been demonstrated that a transient increase in zinc concentrations in and around the nasal cavity prevents rhinovirus binding to cells and disrupts infection (Novick et al 1996) and/or modulates inflammatory cytokines and histamine release that may exacerbate cold symptoms (Kurugöl et al 2007). Additionally, there is evidence to suggest that zinc inhibits viral replication.

Nasal preparations

A randomised, double-blind, placebo-controlled trial with 160 people tested the effects of a nasal spray of 0.12% zinc sulfate and found that it reduced the total symptom score, but had no effect on the duration of cold symptoms or the mean time to resolution (Belongia et al 2001). The effectiveness of intranasal zinc gluconate as a preventative agent against experimentally induced rhinovirus infection was tested in a study of 91 subjects (Turner 2001). It was administered for 3 days prior to rhinovirus inoculation followed by 6 days of treatment. This regimen had no effect on total symptom score, rhinorrhoea, nasal obstruction or the proportion of infected volunteers who developed clinical colds.

Two other trials using a dose of zinc in a nasal gel formulation showed that zinc treatment significantly reduced cold duration compared with placebo when used within 24–48 h of symptom onset (Hirt et al 2000, Mossad 2003). The nasal gel spray contained either 33 mmol/L zinc gluconate or placebo and was administered as one dose per nostril four times daily until symptoms resolved or for a maximum of 10 days. Symptoms that responded included nasal drainage, hoarseness and sore throat (Mossad 2003).

Oral supplements

Both positive and negative results have been obtained for different forms of oral zinc supplements and lozenge preparations. A 2000 Cochrane review analysed the results from seven trials involving 754 cases and concluded that current evidence is inconclusive as to whether zinc lozenges are an effective treatment for symptoms of the common cold (Marshall 2000). This conclusion is considered conservative, as an intention-to-treat analysis at 7 days found a statistically significant relative risk (RR) of 0.69, and the numbers needed to treat for one person to benefit ranged from 4 to 8 (Arroll 2005). The authors of the review were concerned about blinding of the studies and variation in doses used, making a conclusive recommendation difficult.

Since then, several new studies have been published (Eby & Halcomb 2006, McElroy & Miller 2002, 2003, Turner & Cetnarowski 2000). McElroy and Miller (2002) showed that treatment with zinc gluconate glycine lozenges (Cold-Eeze) significantly decreased cold duration (7.5 vs 9.0 days for non-use) and significantly reduced cold frequency and concomitant antibiotic use in school-aged subjects. A subsequent phase IV study by the same pair of researchers (2003) investigated the therapeutic and prophylactic effectiveness of Cold-Eeze for the common cold in a cohort of 134 subjects drawn from the previous study. Once again, zinc gluconate glycine lozenges shortened cold duration (6.9 vs 9.0 days) and the mean number of colds (1.7 vs 1.28), achieving a 25% reduction in cold incidence. Zinc lozenges were administered once daily during the cold season and four times daily as acute treatment. An adult study demonstrated that zinc gluconate (13.3 mg) or zinc acetate (5 or 11.5 mg) lozenges had no effect on duration or severity of cold symptoms (Turner & Cetnarowski 2000). A double-blind, placebo-controlled study found that frequent administration of zinc orotate lozenges (37 mg zinc each) and intranasal zinc gluconate spray had no effects on severity of cold symptoms or their duration (Eby & Halcomb 2006). Another positive finding resulted from a study of oral zinc sulfate syrup administration to 120 otherwise healthy and zinc-replete children aged 1–10 years (median age 5) (Kurugöl et al 2007). A daily dose of 30 mg of elemental zinc was given within 24–48 h after the onset of cold symptoms to those children randomly selected for the treatment group, producing a reduction in symptom severity from day 2. Nasal symptoms were the most significantly improved in those taking zinc; however, the duration of these or other symptoms was not different between the two groups. The study authors note that, in light of the normal serum zinc results at baseline, the actions of zinc are not associated with deficiency correction.

It is not clear why some trials have produced positive results whereas others have not; however, it is suspected that the type of zinc and administration regimen has an influence over effectiveness. A closer look at the evidence shows that zinc gluconate and zinc acetate are the forms generally associated with positive results, whereas other forms are less effective. Additionally, lozenge additives such as sorbitol and citric acid are thought to decrease zinc ion release, which is necessary for zinc's virucidal activity. It has been suggested that zinc lozenges be allowed to completely dissolve in the mouth without chewing and that citrus fruits or juices be avoided 30 min before or after dissolving each lozenge to avoid negating the therapeutic effects of zinc (Silk & LeFante 2005).

Reduced frequency of infections in elderly

Both zinc deficiency, due to poor dietary intake, and impaired cell-mediated immunity are commonly reported in the elderly (>55 years) and have been used to explain the increased infection rates observed in this population. A small randomised double-blind study of zinc supplementation was

undertaken in 50 healthy elderly subjects (Prasad et al 2007). At baseline, plasma zinc values indicated that the majority had a marginal zinc deficiency, while 35% were below the cut-off for frank deficiency. Zinc gluconate supplementation, providing a total daily elemental amount of 45 mg via two divided doses, or placebo was undertaken for 12 months. Those individuals in the treatment group demonstrated a significant reduction in infection incidence (29% vs 88%), with protective effects evident, for example, against upper respiratory tract infections (12% vs 24%), the common cold (10% vs 40%) and influenza (0% vs 12%). Also of note, while no individual in the treatment group experienced more than one infection in the 12-month period, six individuals taking placebo had two infections, and three subjects had three or more infections during the same period. Inflammatory cytokines and markers of oxidative stress were also investigated in this study, confirming zinc's role as both an anti-inflammatory and an antioxidant in the elderly.

Age-related macular degeneration (ARMD)

Both dietary and supplemental zinc have been investigated in the prevention and/or delayed progression of ARMD. A 2005 study found that high dietary intake of zinc, beta-carotene and vitamins C and E was associated with a 35% reduced risk in elderly persons (van Leeuwen et al 2005). Similarly, the Blue Mountains Eye Study, an Australian prospective population-based cohort study conducted over 10 years, demonstrated protective effects of lutein and zeaxanthin but also found that those individuals consuming the highest zinc had an RR of 0.56 for any ARMD and 0.54 for early ARMD compared with all other participants (Tan et al 2008). An interesting study has revealed that increased lifetime exposure to blue light appears to amplify the risk of low dietary antioxidants and zinc (Fletcher et al 2008). Originally believed to simply act as an antioxidant in this condition, ongoing discussions of zinc's possible actions in the prevention of this aetiology have produced new hypotheses.

Smoking has long been established as one of the few independent risk factors for ARMD and a direct association between risk and the number of cigarettes smoked has been elucidated (Coleman et al 2008, Wills et al 2008a). It was revealed that smokers have a four times greater retinal concentration of cadmium than non-smokers and that the associated morphological changes are reasonably consistent with ARMD pathology (Wills et al 2008a). A comparison of zinc and copper concentrations within the retinal pigment epithelium (RPE) and choroid complex of eye donor subjects previously suffering from ARMD and those without the condition has revealed a 23–24% reduction in these metals in afflicted subjects (Erie et al 2009). Furthermore, in vitro studies confirm that zinc and copper, as well as manganese (the latter being most potent), effectively prevent the intracellular concentration of cadmium in retinal tissues and hence modulate its toxicity (Satarug et al 2008, Wills et al 2008b). Taken together with the knowledge that zinc and copper supplementation, in combination with antioxidants, has delayed progression of ARMD, points towards a critical role for metal homeostasis in retinal health.

A 2006 Cochrane review assessed the effects of antioxidant vitamin and/or mineral supplementation on the progression of ARMD and found that evidence of effectiveness is currently dominated by one large trial that showed modest benefit in people with moderate to severe signs of the disease who were administered antioxidant vitamins and zinc together (Evans 2002). The study the authors refer to is the Age-Related Eye Disease Study (AREDS 2001), which showed that high-dose vitamins C and E, beta-carotene, and zinc supplementation delayed the progression from intermediate to advanced disease by 25% over 5 years. The 11 centre, double-blind, prospective study involved 3640 volunteers aged between 55 and 80 years who were randomly divided into four treatment groups, receiving either antioxidant supplements (500 mg vitamin C, 400 international units (IU) vitamin E, and 15 mg beta-carotene daily), zinc oxide and cupric oxide (80 mg elemental zinc, 2 mg elemental copper daily), antioxidants plus zinc, or placebo. The contribution of zinc to this result is unknown (see Lutein monograph for more information about ARMD); however, AREDS2 is currently underway, employing a reduced dose of zinc, in light of interim evidence that a smaller dose may be efficacious and is less likely to produce adverse effects (Coleman et al 2008).

An RCT administered zinc monocysteine (25 mg elemental zinc twice daily) as a stand-alone treatment to 80 ARMD patients over 6 months (Newsome 2008). Those in the treatment group experienced improved visual acuity, contrast sensitivity and reduced macular light flash recovery time when compared with the placebo group, with some benefits evident 3 months into the treatment.

Overall, current evidence suggests that zinc supplementation, either alone or in combination with other antioxidants, may help to prevent ARMD in those at least at moderate risk and delay progression of this condition in those suffering the early stages. Additional emerging evidence suggests an interaction between genetics and responsiveness to zinc as a treatment in ARMD sufferers, with retrospective analyses of the AREDS study demonstrating a strong interaction between those individuals whose progression of the condition was delayed by zinc supplementation and the presence of the complement factor H (CFH) genotype (Klein et al 2008, Lee & Brantley 2008). Substantiation of these findings could assist in the improved targeting of ARMD nutritional therapies.

Diabetes mellitus (T1DM and T2DM)

Zinc is abundant in the pancreas due to extensive roles in both its endocrine and its exocrine functions. During deficiency, this is one of the few tissues that demonstrates reduced concentrations of this mineral (Islam & Loots 2007). Limited data derived from both epidemiological studies and animal models suggest that increased dietary zinc intake may be protective against the development

of both types of diabetes (Bolkent et al 2009, Islam & Loots 2007, Sun et al 2009). Current thoughts regarding zinc's actions in this condition are that attributed to an antioxidant role, conveyed both directly and indirectly, via metallothionein induction (Islam & Loots 2007). Decreasing oxidative stress, zinc would thereby protect beta cells from damage and also assist in maintaining normal insulin secretion.

Zinc supplementation is sometimes used in order to avoid deficiency, a state associated with both T1DM and T2DM (Cunningham et al 1994). It remains unclear, however, whether zinc repletion or using high-dose zinc to induce other effects will be beneficial in the clinical management of diabetes, its complications or its prevention, as current data from both animal and human studies have produced varied results (Baydas et al 2002, Cunningham et al 1994, Farvid et al 2004, Gupta et al 1998, Niewoehner et al 1986, Roussel et al 2003, Tobia et al 1998).

Several intervention studies of oral zinc have produced positive results in T1DM populations, with evidence of reduced glycated haemoglobin amongst individuals in one treatment group (30 mg/day elemental zinc for 3 months) vs the control group (Al-Maroof & Al-Sharbatti 2006), improved blood lipid profiles following 12 weeks of zinc treatment (100 mg/day zinc sulfate) in another study (Partida-Hernández et al 2006) and improved glycaemic control and diabetic neuropathy in 20 patients administered 660 mg/day zinc sulfate over 6 weeks (Hayee et al 2005).

With respect to T2DM, a prospective, double-blind, clinical interventional study of 56 obese women with normal glucose tolerance randomised subjects to treatment with zinc, 30 mg/day, or placebo for 4 weeks (Marreiro et al 2002). Zinc treatment decreased insulin resistance from 5.8 to 4.3 and insulin decreased from 28.8 to 21.2 mU/mL, but was unchanged in the placebo group. These results are particularly noteworthy because the women were not zinc deficient, suggesting a therapeutic role for zinc. Another small study of metformin-resistant T2DM patients administered zinc (zinc acetate 50 mg/day) in combination with melatonin (10 mg/day) ± metformin to two treatment groups and placebo to a third (Hussain et al 2006). This combined treatment proved effective in improving fasting and postprandial glucose levels and augmented the action of the hypoglycaemic drug. Further studies with larger sample sizes are required to validate zinc as an effective treatment in T1DM and T2DM and elucidate the optimal dosing and administration regimen.

Clinical note — Zinc deficiency and diabetes

Diabetes affects zinc homeostasis in many ways and is associated with increased urinary loss, decreased absorption and decreased total body zinc (Chausmer 1998, Cunningham et al 1994). The role of zinc and zinc deficiency in diabetes and its complications or prevention is currently unclear. It has been suggested that deficiency may exacerbate destruction of islet cells in T1DM and may adversely affect synthesis, storage and secretion of insulin, a process that requires zinc. Furthermore, evidence indicates that T1DM patients have a higher concentration of free radicals than healthy controls, which is due to increased oxidant production and/or decreased efficiency of endogenous antioxidant systems (Davison et al 2002). It is suspected that deficiency of key micronutrients (i.e. zinc, copper, manganese and selenium), which are integral components of important antioxidant systems, may be partly responsible.

Improves wound healing

Zinc is an essential co-factor in both wound healing and immune function. Therefore, zinc deficiency retards both fibroplasia and epithelialisation, and results in delayed wound healing in spite of maintained skin stores of zinc, except in instances of severe concomitant protein restriction (Lansdown et al 2007). Zinc supplements are used to restore zinc status in cases of wound healing associated with malnutrition and deficiency. Additionally, zinc administered orally or topically to wounds can promote healing and reduce infection, according to one major review (Lansdown 1996).

Oral application

In 2001, a randomised study demonstrated that oral zinc sulfate significantly improved healing of cutaneous leishmaniasis (Sharquie et al 2001). Results showed that the cure rate for a dose of 2.5 mg/kg was 83.9%, for 5 mg/kg it was 93.1% and for 10 mg/kg it was 96.9%, whereas no lesions showed any sign of healing in the control group. The results of several studies suggest a specific role for oral zinc in surgical wound repair (Lansdown et al 2007). Zinc redistribution and sequestration in the liver occur following both surgical trauma and infection. The corresponding reduction in serum zinc may then impair the individual's healing capacity, as demonstrated in a study of 80 total hip replacement patients (mean age 66 years), in whom serum zinc levels were significantly related to rates of infection and dehiscence (Lansdown et al 2007). Similarly, an interventional study of pre- and postoperative zinc infusion (30 mg/day) in patients undergoing major vascular reconstructive surgery attenuated the anticipated decline in serum zinc and produced significantly fewer wound-healing complications than placebo.

Topical application

Theoretically, topical zinc treatment is most suited to human wound healing that necessitates epithelialisation, e.g. suction blister wound, superficial small incision and split thickness skin graft donor sites. While clinical trials have demonstrated its efficacy in relation to treatment of leg ulcers, pressure ulcers, diabetic foot ulcers and burn wounds (Lansdown et al 2007), one study also demonstrated that *Staphylococcus aureus* was cultured significantly less frequently in zinc oxide treated wounds, which points to the additional antiseptic action. Topical

zinc oxide promotes cleansing and re-epithelialisation of ulcers and reduces the risk of infection and deterioration of ulcers compared with placebo, according to one double-blind trial of leg ulcer patients with low-serum zinc levels (Agren 1990). Evidence from animal and in vitro research suggests that topically applied zinc solution is more effective when combined with iron than when used alone, and can effectively enhance healing in acute partial-thickness and second-degree burn wounds (Feiner et al 2003). The form of zinc used topically may be of marked importance, with some studies investigating high concentrations of zinc sulfate delaying healing and increasing dermal inflammatory cell infiltration (Lansdown et al 2007). Preparations such as zinc oxide may be more suitable than readily water-soluble forms, providing a sustained release of bioavailable zinc at non-cytotoxic levels. Interestingly, pharmacopoeias attribute various zinc forms with different qualities/actions, e.g. zinc sulfate is regarded as a local astringent and antiseptic, insoluble zinc oxide as a mild antiseptic, astringent and protective agent, particularly indicated in inflamed skin and wounds.

Arterial and venous leg ulcers

Chronic leg ulcer patients often exhibit abnormal zinc metabolism and depressed serum concentrations (Lansdown et al 2007). A 2000 Cochrane review assessed six placebo-controlled trials of zinc sulfate supplementation (≥220 mg administered three times daily) in arterial and venous leg ulcers and concluded that, overall, there is no evidence of a beneficial effect on the number of ulcers healed. However, there is some evidence that oral zinc might improve healing of venous ulcers in people with low-serum zinc levels (Wilkinson & Hawke 2000).

Double-blind studies producing encouraging results have used oral zinc (600 mg/day) combined with topical treatment and compression bandages (Haeger & Lanner 1974, Hallbook & Lanner 1972).

Acne and other skin conditions

Over the past 2–3 decades, tetracyclines and macrolide antibiotics have been widely prescribed for the treatment of acne; however, resistance has been reported, especially to erythromycin and clindamycin with cross-resistance being widespread among strains of *Propionibacterium acnes*. As a result, non-antibiotic treatments such as topical and oral zinc preparations have been investigated as both alternatives and adjuncts to these treatments.

Overall, studies have yielded conflicting results, possibly due to considerable placebo effects, with better effects generally seen on inflammatory lesions than other lesion types. This is most likely due to the fact that zinc has a marked anti-inflammatory effect, which was first observed with zinc sulfate and later with zinc gluconate, which is a better tolerated form.

Oral supplementation

Numerous studies have been conducted investigating the effects of zinc supplementation in acne vulgaris (Dreno et al 1989, 1992, 2001, Goransson et al 1978, Hillstrom et al 1977, Orris et al 1978, Weimar et al 1978, Weismann et al 1977, Verma et al 1980). Doses between 90 mg and 200 mg (30 mg elemental zinc) daily taken over 6–12 weeks have been associated with generally positive results, whereas larger doses tend to be poorly tolerated. An open study involving 30 subjects with inflammatory acne found that a lower dose of oral zinc gluconate (30 mg) taken daily reduced the number of inflammatory lesions after 2 months, regardless of whether *P. acnes* was present (Dreno et al 2005).

Two double-blind studies have compared the effects of oral zinc supplementation with two antibiotic medicines, minocycline or oxytetracycline, over 3 months (Cunliffe et al 1979, Dreno et al 1989). Zinc sulfate (135 mg) was as effective as oxytetracycline after 12 weeks' use, decreasing acne scores by 65% in one study, whereas the same dose was not as effective as minocycline (500 mg) in the second study.

Zinc has also been investigated as an adjunct to antibiotic therapy under laboratory conditions. When administered in combination with erythromycin, it inhibits erythromycin-resistant propionibacteria according to two in vitro studies (Dreno et al 2005, Oprica et al 2002).

Topical application

A number of studies have investigated the effects of a topical erythromycin–zinc acetate formulation (Bojar et al 1994, Feucht et al 1980, Habbema et al 1989, Morgan et al 1993, Pierard & Pierard-Franchimont 1993, Pierard-Franchimont et al 1995, Schachner et al 1990)

Statistically significant effects have been observed within the first 12 weeks of treatment for acne severity grades, and for papule, pustule and comedo counts, with the effect of the combination superior to preparations containing erythromycin alone (Habbema et al 1989, Schachner et al 1990). Human studies have identified antibacterial activity against *Propionibacterium* spp. in short-term treatment, which is mostly attributed to zinc (Fluhr et al 1999) and sebosuppressive effects (Pierard & Pierard-Franchimont 1993).

Reduced male fertility

Zinc deficiency leads to several clinical signs, such as decreased spermatogenesis and impaired male fertility and, given zinc's pivotal role in DNA transcription, this is not surprising. Furthermore, zinc finger proteins are critical to the genetic expression of steroid hormone receptors. Together with zinc's additional anti-apoptotic and antioxidant actions, these effects make zinc a promising contributor to healthy sperm (Ebisch et al 2007). The relationship between zinc concentrations in seminal fluid and semen fertility, however, remains somewhat unclear.

When zinc deficiency is not present, a 2002 survey found no statistically significant relationship between zinc in seminal plasma or serum and semen quality or local antisperm antibody of the IgG or IgA class (Eggert-Kruse et al 2002). Furthermore, zinc levels did not influence sperm capacity to penetrate cervical mucus in vitro or in vivo, nor affect

subsequent fertility. However, a study of Chinese men (aged 20–59 years) revealed that when serum zinc concentration was low, the risk of asthenozoospermia increased and the Cu/Zn ratio was higher in those with progressive motility abnormalities (Yuyan et al 2008).

In addition to this, a small number of both animal (Kumar et al 2006) and human supplementation studies (Ebisch et al 2006) have produced contrastingly positive results. The latter study involved 40 sub-fertile and 47 fertile men treated for 26 weeks with 66 mg/day zinc sulfate and 5 mg/day folic acid or placebo, producing a 74% increase in normal sperm count in the sub-fertile subjects; however, more studies with larger sample sizes are required to substantiate these preliminary findings.

Impotence

In men, zinc deficiency may lead to impaired testosterone synthesis, resulting in hypogonadism and impotency. One placebo-controlled study has investigated whether oral zinc supplementation improves erectile dysfunction. The study involved 20 uraemic haemodialysis patients and showed that 6 months treatment with oral zinc acetate (25 mg elemental zinc) taken twice daily 1–2 h before meals resulted in greater libido, improved potency and more frequent intercourse compared to placebo (Mahajan et al 1982). Active treatment also resulted in significant increases in plasma zinc, serum testosterone and sperm count and decreases in serum levels of luteinising hormone (LH) and follicle stimulating hormone (FSH).

Attention-deficit hyperactivity disorder

Zinc deficiency has been implicated in the pathogenesis of attention deficit hyperactive disorder (ADHD) from numerous perspectives. With a critical role in neurological development and evidence of impaired learning and depressed psychomotor retardation in deficiency states, zinc may constitute a direct aetiological cause (Black 2003, Fanjiang & Kleinman 2007). An interesting longitudinal paediatric study found that children with malnutrition (protein, zinc and iron deficiencies) at 3 years of age demonstrated higher externalisation behaviour problems at 8, 11 and 17 years, when compared to replete children (Liu & Raine 2006), with this trifecta of deficiencies, a particularly common combination in young children.

Hypotheses of indirect actions of zinc deficiency include negative behavioural effects mediated via impaired fatty acid metabolism and through the exacerbation of heavy metal effects.

In 1990, Arnold et al observed that boys aged 6–12 years with ADHD and a higher baseline hair zinc level had better responses to amphetamine therapy than children with hair concentrations indicative of mild zinc deficiency. At the time, it was suggested that poor/non-responders to drug therapy and those presenting with suboptimal zinc status would require zinc supplementation instead of amphetamine treatment to address the condition. Since then, numerous controlled studies have identified that children with ADHD have lower zinc tissue levels (serum, red cells, hair, urine, nails) than normal children (Arnold & DiSilvestro 2005). It is not certain why this occurs, but may result from not sitting at the kitchen table long enough to consume a balanced diet, picky eating, stimulant-related appetite suppression, malabsorption or biochemical changes. Since then, zinc status has been also shown to correlate with the amplitude and latency of select brain waves, suggesting that zinc may particularly influence information processing in ADHD children (Yorbik et al 2008).

Three double-blind studies, all conducted in middle-eastern populations, have investigated whether oral zinc supplementation has a beneficial effect in ADHD, producing promising results. One randomised study involving 400 Turkish children with a mean age of 9.6 years found that treatment with 150 mg zinc sulfate (equivalent to 40 mg of elemental zinc) daily for 12 weeks resulted in significant reductions in hyperactive, impulsive and impaired socialisation features, but not in reducing attention deficiency symptoms, as assessed by the ADHD Scale (Bilici et al 2004). A significant difference between zinc and placebo was already evident by week 4 ($P = 0.01$). Older children with low zinc and free fatty acid levels and high body mass index (BMI) responded best to treatment. A second placebo-controlled trial used a combination of 55 mg zinc sulfate (equivalent to 15 mg elemental zinc) and methylphenidate (1 mg/kg) daily for 6 weeks in Iranian children aged 5–11 years and reported significant benefits with the combination (Akhondzadeh et al 2004). Zinc (15 mg/day elemental) or placebo was administered to 218 grade three students in a low-income district of Turkey over 10 weeks, resulting in a reduced prevalence of clinically significant ratings of attention deficit and hyperactivity in the treatment group (Uçkardeş et al 2009).

It is important to note that these studies were conducted with children from countries with suspected widespread zinc deficiency and further investigation is required to determine whether the same beneficial results will occur in children living in Western countries.

Depression

Epidemiological evidence has revealed an inverse relationship between serum zinc and depression rating scores in depressed patients (Nowak et al 2005), the elderly (Marcellini et al 2006) and postpartum women (Wojcik et al 2006). In addition to this, zinc supplementation produces antidepressant-like effects in animal tests and models such as the forced swim test and can augment the action of orthodox antidepressants in these scenarios (Nowak et al 2005). Theories regarding zinc's aetiological role in depression centre on its inhibition of *N*-methyl D-aspartate receptor (NMDA) function and interestingly, suicide victims demonstrate a statistically significant 26% decrease in zinc's antagonistic potency in hippocampal tissue, suggestive of an aberrant interaction between this mineral and the receptor underlying the psychopathology (Nowak et al 2003). Another aspect of interest is the increased inflammatory markers evident in depressed individuals, which would,

through redistribution of zinc, potentially create a pseudo-deficiency (Marcellini et al 2006, Nowak et al 2005).

In spite of growing interest in zinc's antidepressant potential, there has only been one published interventional study to date. Twenty patients with unipolar depression had an improved response to antidepressant medication when taken with zinc aspartate supplements (equivalent to 25 mg elemental daily), according to a small, double-blind pilot study (Nowak et al 2003). Significantly greater reductions in Hamilton Depression Rating Scale scores were achieved with zinc treatment compared to placebo by the 6th week and maintained until the end of the 12-week study.

Diarrhoea

A 2008 Cochrane review of oral zinc treatment for paediatric diarrhoea included 18 trials and 6165 participants (Lazzerini & Ronfani 2008). Typically, the intervention consisted of 10 mg/day of zinc, as either a sulfate, acetate or gluconate salt, administered in a single or divided dose over 2 weeks to children aged 1 month to 5 years presenting with acute or persistent diarrhoea or dysentery. Zinc supplementation consistently reduced the duration and volume of diarrhoea within a few days and while zinc-treated children were significantly more likely to experience vomiting, it was concluded that the benefits of the treatment outweighed this side effect. It is important to note that all except three of these trials were conducted in countries considered to be at high risk of widespread zinc deficiency and in such instances the WHO and UNICEF recommend 10–20 mg/day. This review found no benefit in children less than 6 months old.

Crohn's disease

Although reduced zinc status has been associated with chronic diarrhoea and Crohn's disease (Sturniolo et al 1980), the results from a small open study demonstrated that oral zinc sulfate (110 mg three times daily) resolved intestinal permeability problems in people with increased permeability and decreases relapse rates (Sturniolo et al 2001).

Herpes simplex

In vitro studies confirm that zinc can inhibit the replication of the herpes simplex virus; however, the concentration required is much higher than possible in a physiological context (Overbeck et al 2008). Accordingly, topical preparations have been the most consistently studied with positive results. Overall, application of zinc preparations greatly reduces or eliminates recurrence of genital herpes infections and resolves symptoms of herpes simplex infections (Finnerty 1986, Kneist et al 1995). Zinc sulfate gel applied every 2 h was a more effective treatment than placebo in herpes simplex labialis in a double-blind study of 80 subjects (Kneist et al 1995). Another study of 200 volunteers with herpes simplex found that 0.25% zinc sulfate solution, started within 24 h of lesion appearance and applied 8–10 times daily, cleared lesions within 3–6 days (Finnerty 1986). A randomised, placebo-controlled study using a weak zinc solution (0.05% or 0.025% zinc sulfate) found no effects on frequency, duration or severity of herpes attacks, suggesting that stronger concentrations are required for effectiveness (Graham et al 1985).

Anorexia nervosa

There is evidence that suggests zinc deficiency may be intimately involved with anorexia nervosa, if not as an initiating cause, then as an accelerating or 'sustaining' factor for abnormal eating behaviours that may deepen the pathology of the anorexia in relation to neurological, immunological and metabolic aberrations (McClain et al 1992, Saito et al 2007, Shay & Mangian 2000). Zinc status is compromised in anorexia nervosa due to an inadequate zinc intake, with supplementation (50 mg elemental zinc/day) shown to decrease depression and anxiety, stop body weight loss and improve weight gain (Katz et al 1987, Safai-Kutti 1990). According to one randomised, double-blind, placebo-controlled trial, 100 mg of zinc gluconate (14 mg/day elemental) doubled the rate of subjects with anorexia nervosa increasing their BMI compared to placebo (Birmingham et al 1994). Accordingly, some key researchers advocate for routine prescribing of zinc for a minimum of 2 months in all anorexia nervosa patients (Birmingham & Gritzner 2006).

Improves taste perception

Dysfunctional taste perception, or dysgeusia, is a condition that can at the least affect quality of life (QOL) and occasionally can become life threatening. Research into the aetiology of taste impairment has revealed a long list of possible causes and contributing factors that includes various pathologies and drugs (Brown & Toma 1986, Deems et al 1991, Ikeda et al 2005, Kettaneh et al 2005, Osaki et al 1996, Rareshide & Amedee 1989, Zverev 2004). The pioneer of research in zinc-related taste acuity, Henkin, concluded in 1976 that zinc could not explain all cases of taste impairment (Henkin et al 1976). A subsequent review concurred: 'depletion of zinc can lead to decreased taste acuity but decreased taste acuity is not necessarily associated with depletion of zinc' (Catalanotto 1978).

Impaired gustatory function in the elderly is also well established (Bales et al 1986, Bartoshuk 1989, Deems et al 1991, Greger 1977, Greger & Geissler 1978, Ikeda et al 2005, Kettaneh et al 2005, Sandstead et al 1982, Schiffman 1983), particularly in relation to salt perception (Bales et al 1986, Greger & Sickles 1979, Sandstead et al 1982). Although zinc status also characteristically declines with age (Bales et al 1986, Greger 1977, Greger & Geissler 1978, Sandstead et al 1982), many studies have failed to demonstrate a consistent correlation between the two phenomena. While this has been challenged by the findings of a study (Stewart-Knox et al 2005), previous large-scale studies of elderly patients presenting with hypogeusia or ageusia have indicated that zinc deficiency represents the sole cause in <40% of elderly patients (Deems et al 1991, Ikeda et al 2005). Other major causes of taste impairment in this age group include the effect

of medications and systemic diseases (Deems et al 1991, Ikeda et al 2005, Schiffman 1983). Consequently, confirmation of zinc deficiency in patients with taste impairment is necessary in order to determine the suitability of zinc as a treatment.

Several interventional studies investigating zinc as a treatment for taste impairment have produced generally positive findings. Zinc supplementation of 140 mg of zinc gluconate (20 mg/day elemental) in 50 patients with idiopathic dysgeusia improved gustatory function when compared with placebo (Heckmann et al 2005). In another study of 109 patients with idiopathic taste impairment, including some with low-serum zinc, subjects were randomly assigned to either placebo or one of three zinc treatment groups: 17 mg/day, 34 mg/day or 68 mg/day zinc carnosine for 12 weeks (Sakagami et al 2008). Only those patients receiving 68 mg/day demonstrated significantly improved gustatory sensitivity over placebo. Two studies focussing specifically on improving taste perception in the elderly (Ikeda et al 2008, Stewart-Knox et al 2008) have been successful, particularly in relation to increased salt sensitivity and in one study achieved a 74% response rate for improved gustatory function generally.

In contrast treatment with zinc sulfate (45 mg three times daily) concomitant with and 1 month following radiotherapy treatment in patients suffering from head and neck cancers did not prevent taste alterations typically associated with this treatment and previously speculatively linked with poor zinc status (Halyard et al 2007).

Tinnitus

In addition to its many diverse neurological roles, zinc has specifically been shown to modulate synaptic function in the cochlear nucleus through its involvement with glutamate receptors (Coehlo et al 2007). Also required for production of Cu/Zn SOD, the most abundant antioxidant enzyme in this tissue, zinc has a critical role in its healthy function through control of oxidation and the large amounts of generated reactive oxygen species. There is also evidence that a deficiency of Cu/Zn SOD potentiates ear hair cell degeneration secondary to excessive oxidation damage.

In 1987, a report was published suggesting a link between reduced zinc status and intermittent head noises in people suffering with tinnitus (Gersdorff et al 1987). This has been further investigated in several studies; however, the poorly defined patient groups and use of serum zinc as the means of measuring zinc status makes interpretation of results difficult to assess (Coehlo et al 2007). Results from these studies, however, suggest a non-significant trend of lower serum zinc values for patients suffering this condition compared to healthy controls.

In 1991 Paaske et al reported the results of a randomised, double-blind study of 48 patients with tinnitus that had failed to find a significant effect on symptoms with sustained-release zinc sulfate tablets. Of note, only one subject had low serum zinc levels. A study of 111 subjects aged 20–59 years found that individuals with tinnitus who had normal hearing had significantly lower serum zinc levels than controls, whereas zinc levels were normal for those with accompanying hearing loss (Ochi et al 2003). In addition, a significant correlation between average hearing sensitivity and serum zinc level was observed. Yetiser et al (2002) investigated serum zinc levels and response to supplementation in 40 patients with severe tinnitus of various origins. Some relief in tinnitus symptoms was reported by 57.5% of all subjects who received 220 mg of zinc daily for 2 months; however, the effect was considered minor. When results were divided by age, a different finding emerged as 82% of people over 50 years of age experienced an improvement on the tinnitus scale compared to only 48% of younger subjects. There was no correlation between severity of tinnitus and serum zinc levels. Zinc supplementation (50 mg/day) was further studied in a randomised, placebo-controlled trial involving 41 Turkish patients with tinnitus of no known cause. Active treatment for 2 months produced clinically favourable progress in 46.4% of subjects; however, this result was not statistically significant (Arda et al 2003). A review of these studies concluded that, although hampered by methodological weaknesses, zinc treatment may be beneficial in some tinnitus sufferers and while an optimal dose for zinc has yet to be elucidated, most successful designs have employed 50–66 mg/day of elemental zinc in divided doses (Coehlo et al 2007).

Warts

Oral zinc sulfate (10 mg/kg) supplements administered in three divided doses per day (up to 600 mg/day) for 2 months completely cleared recalcitrant viral warts in 87% of patients, according to a single-blind, placebo-controlled trial of 80 volunteers with at least 15 viral warts that were resistant to other treatments (Al Gurairi et al 2002). Warts were completed cleared in 61% of patients after 1 month of treatment, whereas none of the patients receiving placebo reported a successful response and some developed new warts. In both placebo and treatment groups, the drop-out rates were high: 50% and 45%, respectively. Interestingly, patients in the treatment group with low-serum zinc baseline levels (mean 62.4 microgram/100 mL) exhibited no signs or symptoms of deficiency and zinc serum levels failed to rise in the patients who remained resistant to zinc therapy. Treatment with high-dose zinc supplements was accompanied by nausea and in some cases vomiting and mild epigastric pain, although these symptoms were described as mild and transient.

OTHER USES

Reducing the risk of cancer

Epidemiological studies suggest that zinc deficiency may be associated with increased risk of cancer (Prasad & Kucuk 2002).

HIV and AIDS

Given zinc deficiency most profoundly compromises T-cell function, interest in zinc treatment for HIV and AIDS has been ongoing. Low plasma zinc

concentration occurs in HIV infection, especially with advancing illness (Wellinghausen et al 2000). The balance of evidence favours the view that a low plasma zinc level is a marker for disease progression (Siberry et al 2002). A series of small interventional studies have produced mixed results, some demonstrating improved immune markers and reduced opportunistic infections (Mocchegiani et al 1995, Zazzo et al 1989), while others suggest either no therapeutic effect or increased risk of progression from HIV to AIDS (Tang et al 1996). These contrasting findings have been speculatively attributed to differences in baseline zinc status amongst subjects. One author points out that anti-retroviral treatment has been shown to counteract zinc deficiency and therefore administering zinc to individuals taking this medication may enhance the risk of zinc toxicity and its associated immune impairment (Overbeck et al 2008). Large intervention trials are not available to determine whether zinc supplementation in HIV infection produces positive outcomes.

Malaria

Duggan et al (2005) identified low plasma zinc levels in children with acute malaria, including a significant correlation between evidence of illness severity, CRP levels and zinc status; however, this may be an artifact of the acute phase effects on zinc homoestasis, rather than indicative of genuine depletion (Overbeck et al 2008). Zinc supplementation (10 mg elemental) randomly allocated to preschool children residing in a malaria-endemic region of Papua New Guinea for 6 days a week over 46 weeks reduced morbidity due to *Plasmodium falciparum* (Shankar et al 2000). Further studies have produced contradictory findings in relation to zinc's capacity to prevent malaria while studies of treatment regimen that include zinc as an adjuvant to standard chemotherapy have found no benefit (Overbeck et al 2008).

Pneumonia

A randomised, placebo-controlled trial in which 1665 children aged less than 12 months were given 70 mg of zinc prophylactically found a reduced incidence of pneumonia (17%), with severe pneumonia incidence reducing by 49%. It also reduced upper respiratory tract infection (URTI) by 8% and reactive airways disease (bronchiolitis) by 12% (Brooks et al 2005). Serum zinc concentrations have been shown to be negatively correlated with pneumonia incidence in a study of nursing home residents, prompting researchers to consider zinc as a potential prophylactic in this population also; however, there are currently no RCTs (Overbeck et al 2008).

A randomised, controlled trial involving 270 children aged between 6 and 12 months, hospitalised with pneumonia, found that those given 20 mg/day of zinc (as acetate) showed significant reductions in recovery time from severe pneumonia. Overall hospital stay duration was also reduced when used with standard antimicrobial therapy (Brooks et al 2004). Results from a similarly designed study, however, failed to corroborate zinc as an effective treatment (Bose et al 2006). The results of Coles et al may help to clarify these disparate findings (2007). While investigating the efficacy of adjunctive zinc treatment (10 mg zinc sulfate administered twice daily) in paediatric patients (<2 years) hospitalised for severe pneumonia, the researchers differentiated between bacterial and non-bacterial aetiologies. In doing so, it became apparent that zinc supplementation in bacterial pneumonia detrimentally affected recovery prolonging hospital stays, etc — an effect not seen in the non-bacterial cases. This may be explained by the negation of the acute phase response's sequestering of zinc in the liver and gives weight to the argument that zinc supplementation should be avoided in such scenarios, as increased availability of this mineral to the pathogen may facilitate its growth and replication (Calder 2002)

Wilson's disease

Patients with diagnosed Wilson's disease have increased hepatic glutathione and reduced oxidation when supplemented with zinc sulfate (220 mg three times daily) for 3 months, compared with those using penicillamine (Farinati et al 2003).

Alzheimer's dementia

Cognitive performance was temporarily improved after 3 months of zinc supplementation (zinc chelate 15 mg) taken twice daily by six subjects with Alzheimer's disease (Potocnik et al 1997). Although the initial improvement was not maintained in this small open study, a modest cognitive improvement on psychometric testing was observed at 12 months for the four patients evaluated.

DOSAGE RANGE

Australian RDI

Children
- 1–3 years: 3 mg/day.
- 4–8 years: 4 mg/day.
- 9–13 years: 6 mg/day.
- Males 14–18 years: 13 mg/day.
- Females 14–18 years: 7 mg/day.

Adults
- Males >19 years: 14 mg/day.
- Females >19 years: 8 mg/day.

Pregnancy
- <19 years: 10 mg/day.
- ≥19 years: 11 mg/day.

Deficiency
- 25–50 mg elemental zinc daily.

According to clinical studies

- Common cold — zinc gluconate lozenges (free of sorbitol, mannitol or citric acid).
  - Adults: 9–24 mg elemental zinc dissolved in the mouth, without chewing every 2 hours for acute treatment.

  - School-aged children: dissolved in the mouth once daily as prophylaxis and four times daily for acute treatment.
    It is recommended that citrus fruits or juices be avoided 30 minutes before or after dissolving each lozenge to avoid negating the effects of zinc.
- Improved immune function in elderly — 45 mg/day elemental zinc as zinc gluconate.
- Common cold — nasal gel spray containing either 33 mmol/L zincum gluconicum administered four times a day for a maximum of 10 days.
- Pneumonia — 70 mg/day prophylactically or 20 mg/day in children suffering acute infection. Malaria — 10 mg/day elemental zinc.
- ARMD — zinc oxide (equivalent to 80 mg elemental zinc), together with 500 mg vitamin C, 400 IU vitamin E and 15 mg beta-carotene, taken daily or 50 mg/day of zinc as zinc monocysteine as stand-alone treatment.
- ADHD — 55–150 mg zinc sulfate daily.
- T1DM— 30 mg/day (type of zinc unknown).
- T2DM – 50 mg/day zinc acetate.
- Wound healing — 2.5 mg/kg zinc sulfate daily, zinc oxide form preferable, topically.
- Leg ulcers — 600 mg zinc sulfate daily.
- Male fertility — 60 mg/day of zinc sulfate and 5 mg/day as folic acid.
- Acne vulgaris — 90–200 mg (50 mg elemental) daily.
- Crohn's disease — 110 mg zinc sulfate taken three times daily.
- Diarrhoea — 10–20 mg/day elemental zinc in children <5 years for 2 weeks.
- Herpes infection — 0.25% zinc sulfate solution applied 8–10 times daily.
- Anorexia nervosa — 14–50 mg elemental zinc daily.
- Dysgeusia — 20 mg/day elemental zinc as zinc gluconate and 68 mg/day as zinc carnosine.
- Tinnitus — 50–200 mg daily of zinc (salt unknown).
- Warts — 10 mg/kg zinc sulfate taken orally in three divided doses (up to 600 mg/day) for 1–2 months.

TOXICITY

Signs of toxicity are nausea, vomiting, diarrhoea, fever and lethargy and have been observed after ingestion of 4–8 g zinc according to a 2002 WHO report. Single doses of 225–450 mg of zinc usually induce vomiting (King 2003).

Doses of zinc ranging from 100 to 150 mg/day interfere with copper metabolism and cause hypocuprinaemia, red blood cell microcytosis and neutropenia if used long term.

ADVERSE REACTIONS

Mild gastrointestinal distress has been reported at doses of 50–150 mg/day of supplemental zinc (King 2003). According to a randomised, double-blind study, zinc gluconate glycine lozenge (104 mg equivalent to 13.3 mg ionic zinc) taken every 3–4 h is well tolerated (Silk & LeFante 2005). Of the side effects that were reported, dry mouth and a burning sensation on the tongue were probably related to use, whereas symptoms of nausea, dizziness, lightheadedness and upset stomach were considered as possibly related.

SIGNIFICANT INTERACTIONS

Calcium

High levels of dietary calcium impair zinc absorption in animals, but it is uncertain whether this occurs in humans — separate doses by 2 h.

Captopril and enalopril

These drugs increase urinary excretion of zinc (Golik et al 1990). Monitor for signs and symptoms of zinc deficiency. Increased zinc intake may be required with long-term drug treatment.

Coffee

Coffee reduces zinc absorption — separate intakes by 2 h (Pecoud et al 1975).

Copper

High zinc intakes (100–150 mg/day) interfere with copper metabolism and can cause hypocuprinaemia with long-term use. Avoid using high-dose zinc supplements long term, or increase intake of copper.

Folate

Folate intake may reduce zinc levels — observe patient for signs and symptoms of zinc deficiency with long-term folate supplementation.

Iron

Supplemental (38–65 mg/day elemental) iron decreases zinc absorption (King 2003) — separate doses by 2 h.

Non-steroidal anti-inflammatory drugs (NSAIDs)

Zinc interacts with NSAIDs by forming complexes with these drugs (Dendrinou-Samara et al 1998) — separate dose by 2 h.

Tetracyclines and quinolones

Complex formation between zinc and tetracycline results in reduced absorption of both substances with potentially reduction in efficacy — separate dose by 2 h.

Thiazide and loop diuretics

These diuretics increase urinary zinc loss — monitor for signs and symptoms of zinc deficiency with long-term drug use. Increased zinc intake may be required with long-term therapy.

Methylphenidate

The efficacy of this drug is improved by supplementation with zinc sulfate (15 mg elemental zinc) for 6 weeks in children with ADHD. There is no change to side effects reported (Akhondzadeh et al 2004).

Vaccinations

Zinc acetate improved seroconversion of vibriocidal antibodies in children given a cholera vaccination (Albert et al 2003) in both faecal and serum titres (Karlsen et al 2003).

Radiotherapy
Radiotherapy reduces plasma zinc levels (Ertekin et al 2004). Supplementation may be required with intensive radiotherapy treatment.

Interferon-alpha/ribavirin
Interferon-alpha and ribavirin treatment for hepatitis C patients is not affected by zinc supplementation (Ko et al 2005).

Orlistat
Orlistat has no significant effect on zinc levels (Zhi et al 2003).

Tricyclic antidepressants and selective serotonin reuptake inhibitors
Zinc supplementation (25 mg elemental zinc daily) improves the efficacy of antidepressants such as tricyclic antidepressants and SSRIs after 2 weeks of intervention (Nowak et al 2003) — beneficial interaction possible.

CONTRAINDICATIONS AND PRECAUTIONS
Amiloride reduces zinc excretion and can lead to zinc accumulation (Reyes et al 1983). Therefore, supplementation should be used with caution.

PREGNANCY USE
Zinc is safe in pregnancy and may improve fetal heart rate in zinc-deficient mothers (in conjunction with iron and folic acid) (Merialdi et al 2004).

PRACTICE POINTS/PATIENT COUNSELLING
- Zinc is involved in many chemical reactions that are important for normal body functioning and it is essential for health and wellbeing.
- Although zinc supplements are traditionally used to treat deficiency, they are also used to prevent deficiency in conditions associated with low zinc status or deficiency, such as acrodermatitis enteropathica, anorexia nervosa, malabsorption syndromes, conditions associated with chronic diarrhoea, alcoholism, diabetes, HIV and AIDS, recurrent infections, severe burns, Wilson's disease and sickle cell anaemia.
- Zinc supplements are also popular among athletes in order to counteract zinc loss that occurs through perspiration.
- Zinc lozenges have been used to prevent and treat the symptoms of the common cold and oral supplements have been used to treat acne vulgaris, improve wound healing and chronic leg ulcers, resolve intestinal permeability problems and reduce recurrences in Crohn's disease, treat recalcitrant warts, reduce symptoms of tinnitus and improve ADHD.
- Topical applications of zinc have been used to treat acne vulgaris (in combination with erythromycin), herpes simplex and to promote wound healing.
- Numerous interactions exist between other minerals, foods and medicines and zinc.

PATIENTS' FAQs
What will this supplement do for me?
Zinc is found in every cell of the body and is essential for health and wellbeing. Some studies have found that supplements are not only useful to treat and prevent deficiency, but may also be useful in conditions such as the common cold, poor wound healing and leg ulcers, diabetes, Crohn's disease, acne vulgaris, warts, ADHD and tinnitus. Topical preparations may be useful in acne vulgaris (with erythromycin), herpes infection and chronic wounds.

When will it start to work?
This depends on the indication (refer to monograph for more details).

Are there any safety issues?
Used in high doses, zinc can cause nausea, vomiting, gastrointestinal discomfort and, if used long term, reduce copper levels. Zinc also interacts with a number of other minerals, foods and medicines.

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APPENDIX 1

GLOSSARY AND ABBREVIATIONS

Abortifacient – Substance used to terminate a pregnancy.
ACE – angiotensin-converting enzyme
ACM – all-cause mortality
ACTH – adrenocorticotropic hormone
Active constituents – Chemical components that exhibit pharmacological activity and contribute to the agent's overall therapeutic effects.
Acute – Beginning abruptly; sharp and intense; subsiding after a short period.
Adaptogen – Innocuous agent, non-specifically increasing resistance to physical, chemical, environmental, emotional or biological factors ('stressors') and having a normalising effect independent of the nature of the pathological state.
ADHD – attention deficit hyperactivity disorder
ADI – acceptable daily intake
Adjuvant – Substance added to a mixture to enhance the effect of the main ingredient.
ADR – adverse drug reaction
ADRAC – Adverse Drug Reactions Advisory Committee (Australia)
Adverse reaction – Unintended harmful, undesirable or seriously unpleasant response to a medicine at doses intended for prophylaxis, diagnosis or therapeutic effect.
Aerial parts – All parts of a plant that are above the ground. Very often, plants that have useful aerial parts are harvested when flowering (e.g. St John's wort — *Hypericum perforatum* of the Hypericaceae family).
Agonist – Substance that binds to and activates a receptor, thereby causing a response.
Alkaloid – Naturally occurring cyclic organic compound containing nitrogen in a negative oxidation state, which has limited distribution in living organisms. Based on their structures, alkaloids are divided into several subgroups: non-heterocyclic alkaloids and heterocyclic alkaloids, which are again divided into 12 major groups according to their basic ring structure. They tend to have marked physiological effects in vivo (e.g. morphine, codeine, nicotine).
Allostatic responses – Changes that occur in the body in order to adapt and respond to physical or psychological change (e.g. standing, sitting, stress). They are critical to survival, have broad boundaries and involve the sympathetic nervous system and the hypothalamus–pituitary–adrenal axis.
ALT – alanine aminotransferase
Amino acid – Organic compound composed of one or more basic amino groups and one or more acidic carboxyl groups; form the basic structural units of protein.
AMP – adenosine monophosphate
Analgesic – Substance that relieves the symptoms of pain.
ANF – atrial natriuretic factor
Antagonist – Substance that binds to a receptor (blocking others from doing so), but does not activate it, causing a diminished response.
Anthelmintic – Substance that destroys or assists in the expulsion of intestinal worms.
Anthocyanins – Compounds responsible for the bright colours of most flowers and fruits; water-soluble pigments that occur as glycosides and their aglycones (anthocyanidins) and have significant antioxidant activity.
Anti-allergic – Substance that reduces the allergic response (e.g. antihistamine activity or mast-cell stabilisation).
Anti-asthmatic – Substance that prevents asthma attacks and/or reduces their severity.
Anti-emetic – Substance or procedure that prevents or alleviates nausea and vomiting.
Anticholinergic – Agent that blocks cholinergic receptors (e.g. atropine), which results in inhibition of transmission of parasympathetic nerve impulses.
Anticoagulant – Substance that prevents or delays blood coagulation (e.g. warfarin).
Antidiabetic – Substance that aids in blood glucose management or improves management of diabetes via other mechanisms.
Antigen – Substance that the body recognises as foreign and to which it can evoke an immune response; often it is a protein.
Antimicrobial – Substance that kills microorganisms or inhibits their growth or replication.
Antioxidant – Substance that inhibits or delays the oxidation of a second substance; also described as scavenging free-radical molecules.

Antiplatelet – Substance that inhibits platelet aggregation and thereby prolongs bleeding time (e.g. aspirin).
Antipruritic – Substance or procedure that relieves or prevents itching.
Antipyretic – Substance or procedure that reduces fever.
Antispasmodic – Substance that reduces smooth muscle spasms.
Antitussive – Substance that suppresses the cough reflex.
Anxiolytic – Substance used to treat and relieve anxiety states.
Apolipoprotein – Protein on the surface of lipoproteins that may bind to receptors, activate enzymes involved in lipoprotein metabolism and provide structure.
Apoptosis – Programmed cell death.
ARMD – age-related macular degeneration
AST – aspartate aminotransferase
Astringent – Substance that precipitates proteins, causes vasoconstriction and constriction of mucous membranes, and reduces cell permeability when applied topically.
ATP – adenosine triphosphate
Bark – Outermost protective layer of a tree trunk, formed by layers of living cells just above the wood itself. There are usually high concentrations of the active ingredients in the bark (e.g. cinnamon from *Cinnamomum camphora* of the Lauraceae family).
Bioavailability – Proportion of an administered dose that reaches the systemic circulation intact.
Bitter tonic – Herbs with a bitter taste, which are used to stimulate the upper gastrointestinal tract (i.e. stomach, liver, pancreas). They stimulate appetite and digestive function.
BMD – bone mineral density
BMI – body mass index
BPH – benign prostatic hypertrophy
Bulb – Fleshy structure made up of numerous layers of bulb scales, which are leaf bases. Bulbs that are popular for medicinal use include onion and garlic (*Allium cepa* and *A. sativum*, respectively, both of the Liliaceae family).
BZM – bortezomib
CAM – complementary and alternative medicine
Cardioprotective – Substance that protects the heart from damage by toxins or ischaemia (oxygen deficiency).
Carminative – Substance that relieves flatulence, abdominal distension, spasm and discomfort by relaxing the intestinal muscles and sphincters.
Carotenoid – Group of red, yellow or orange highly unsaturated pigments found naturally in foods. Some are converted to vitamin A in the body and most exhibit antioxidant properties.
CFS – chronic fatigue syndrome
Chelation – Chemical interaction of a metal ion with another substance, which results in the formation of a molecular complex with the metal firmly bound and isolated.
Chemoprevention – Substance or intervention that reduces the incidence of cancer.
Cholagogue – Substance that stimulates the release of stored bile from the gall bladder.
Choleretic – Substance that stimulates both the production and the flow of bile.
Chronic – Persisting for a long period of time.
Chylomicrons – Large particles that transport dietary cholesterol and fatty acids from the gastrointestinal tract to the liver.
CMEC – Complementary Medicines Evaluation Committee
CMs – complementary medicines
CNS – central nervous system
Cognitive activator – Substance or procedure that stimulates the mental processes such as memory, judgment, reasoning and comprehension.
Cohort study – Study concerning a specific population that shares a common characteristic (e.g. same age, same gender).
Cold extraction – Process in which plant material is extracted in a solvent of differing polarity at room temperature, which enables maximum extraction of most components.
Contraindication – Any factor that makes it undesirable or dangerous to administer a medicine or perform a procedure on a specific patient.
Corticosteroids – Steroidal hormones that are synthesised and released from the adrenal cortex; includes both glucocorticoids and mineralocorticoids.
COX – cyclo-oxygenase
CPI – consumer product information
CRP – C-reactive protein
Crude herb – Raw plant before it is processed or dried.
CVD – cardiovascular disease
Cytochrome P450 (CYP) – Proteins involved in extra-mitochondrial electron transfer, chiefly in the liver and during detoxification. There are many CYPs; they are named by the root symbol CYP, followed by a number for family, a letter for subfamily, and another number for the specific gene.
DBP – diastolic blood pressure
Debridement – Removal of foreign objects, damaged tissue, cellular debris and dirt from a wound or burn to prevent infection and promote healing.
Decoction – Aqueous medicine made from an extract of water-soluble substances, usually with the aid of boiling water.
Decongestant – Substance or procedure that reduces or eliminates congestion and swelling, usually of mucous membranes.
Demulcent – Substance that soothes and reduces irritation of tissues such as skin or mucous membranes.
DHA – docosahexanoic acid
DHEA – dehydroepiandrosterone
Diuretic – Substance that modifies kidney function to increase the rate of urine flow.
DMBA – 7,12-dimethylbenz[a]anthracene
Double-blind study – Study in which neither the test subject nor the clinician knows whether a placebo or active medicine is being administered. The substances are often identifiable by a code that is revealed

after results are obtained. This method is widely used in clinical studies to confer greater objectivity.
DSM-IV–*Diagnostic and Statistical Manual [of Mental Health Disorders]*, 4th edn.
EAR–estimated average requirement
EBM–evidence-based medicine
ECG–electrocardiogram
EEG–electroencephalogram
EGCG–epigallocatechin-3-gallate
Emmenagogue–Substance that increases the strength and frequency of uterine contractions, and initiates and promotes menstrual flow (some are also abortifacients).
Emollient–Substance that softens tissue and reduces irritation, usually of the skin and mucous membranes.
Endogenous–Originating from within the body; synthesised by the body.
Epidemiological study–Study of occurrence and distribution of disease in large human populations.
Ergogenic aid–Substance that improves energy utilisation with the expectation that it will enhance physical performance.
Erythropoiesis–Process of erythrocyte production in the bone marrow.
ESADDI–estimated safe and adequate daily dietary intake
ESCOP–European Scientific Cooperative on Phytotherapy
ESR–erythrocyte sedimentation rate
Essential amino acids–Eight amino acids that are required for health and must be obtained from the diet: isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan and valine.
Essential fatty acids (EFA)–Polyunsaturated acids that are required for growth and general health and must be obtained from the diet (e.g. omega 3 EFAs found in fish oils).
Essential oil–Volatile oils usually extracted from plants through a process of either steam distillation or microwave extraction. They consist of terpenes (mono- and sesquiterpenoids and coumarins) and are of considerable importance as active ingredients (e.g. peppermint oil from *Mentha* × *piperita* from the Lamiaceae family).
Expectorant–Substance that promotes the expulsion of mucus, fluids or sputum from the respiratory tract.
Extract–Substance prepared by the use of solvents or evaporation to separate it from the original material.
Fatty oils–Non-volatile, insoluble oils pressed from either the seeds or the fruits of a plant (e.g. olive oil).
FDA–Food and Drug Administration (USA)
FEV_1–forced expiratory volume in 1 second
Flavonoids–Compounds responsible for the colour of flowers, fruits and sometimes leaves. The name derives from the Latin *flavus*, meaning yellow. Some may contribute to the colour as co-pigment. Flavonoids protect the plant from UV damage and play a role in reproduction by attracting pollinators.
Flowers–Commonly used in medicine (e.g. cloves (*Syzygium aromaticum*, Myrtaceae family), chamomile (*Chamomilla recutita*, Asteraceae family) and marigold (*Calendula officinalis*, Asteraceae family)).
Fluid extract–Hydro-ethanolic extract of crude herbal material with a drug solvent ratio of 1:1 or 1:2 (e.g. 1 part herb to 1 or 2 parts solvent).
Free radical–Unstable organic compound with at least one unpaired electron.
Fresh plant tincture–Herbal extract made from fresh plant instead of dried material.
Fruit–Most commonly used seeds are anis (*Pimpinella anisum*) and fennel (*Foeniculum vulgare*), both of the Apiaceae family. In some instances, the fruit peel is used specifically (e.g. citrus spp, from the Rutaceae family).
FSH–follicle stimulating hormone
FVC–forced vital capacity
GABA–gamma-aminobutyric acid
GAD–generalised anxiety disorder
Galactogogue–Substance that promotes the production and flow of breast milk.
GI–glycaemic index
GLUT–glucose transporters
Glycoside–Sugar-containing compound with a glycone (sugar) and aglycone (non-sugar) components that can be cleaved on hydrolysis.
GSH–glutathione
Gum–Solids consisting of mixtures of polysaccharides that are water-soluble and are partially digested by humans. Gums sometimes flow from a damaged plant stem as a defence mechanism or sometimes as a protective system against the invasion of bacteria and fungi. Well-known examples are gum arabic (*Acacia senegal*, Leguminosae), and aloe gel (*Aloe vera*, Liliaceae family: gum mixed with water).
Gy–gray (unit of radiation)
Haemostasis–Physiological process that stops bleeding (i.e. vessel constriction, platelet plug formation and blood coagulation).
HbA_{1c}–haemoglobin A_{1c}
HBeAg–hepatitis B early antigen
HDL–high-density lipoprotein
Hepatoprotective–Substance that reduces or prevents liver damage; protects against the destructive effect of hepatotoxins.
High-performance liquid chromatography–Very popular and widely used method for the analysis and isolation of bioactive natural products.
HIV–human immunodeficiency virus
HMG-CoA–3-hydroxy-3-methylglutaryl coenzyme A
HPA–hypothalamus–pituitary–adrenal [axis]
HRT–hormone replacement therapy
HSV–herpes simplex virus
Hypnotic–Substance that induces sleep or the feeling of dreamy sleepiness.
Hypoglycaemic–Substance that reduces blood glucose levels.
Hypolipidaemic–Substance that reduces blood levels of lipids (e.g. cholesterol, triglycerides).
Iatrogenic–Condition caused by medical or surgical treatment or diagnostic procedures.
IBS–irritable bowel syndrome
IFN–interferon
Ig–immunoglobulin

IL–interleukin
IM–integrative medicine
Immunomodulation–Substance that alters the immune response; also described as having a balancing effect on immune responses.
Immunostimulant–Substance that augments the immune response.
Immunosuppressant–Substance that inhibits the immune response.
Infused oil–Herbal extract using a fixed oil as the solvent.
Infusion (herbal)–Herbal tea prepared by pouring boiling water over plant parts and steeping for a short time.
iNOS–inducible nitric oxide synthase
Inotrope–Substance that has an effect on the force of myocardial contractility. A positive inotrope increases the force of contraction whereas a negative inotrope decreases the force of contraction.
INR–international normalised ratio
Interaction–Pharmacological interaction is said to occur when the response to one medicine varies from what is usually predicted because another substance has altered the response. An interaction may lead to drug toxicity or a loss of drug effect; however, it can also be manipulated to benefit the patient by improving outcomes, reducing side effects or reducing drug dose and costs.
IO–integrative oncology
IP–intraperitoneal
IQ–intelligence quotient
Ischaemia–Oxygen deficiency.
IV–intravenous
IVF–in vitro fertilisation
Laxative–Substance that causes bowel evacuation.
LD_{50}–median lethal dose
LDL–low-density lipoprotein
LH–luteinising hormone
LOHAS–lifestyles of health and sustainability
Maceration–Method of herbal extraction in which cut herb is soaked in solvent (such as cold water) for a period of time before draining, straining and pressing.
Meta-analysis–Quantitative statistical procedure for combining the results of independent studies to better analyse the efficacy of a specific treatment.
Mineral–Compound containing a non-metal, metal, radical or phosphate required for proper body functioning and health maintenance.
Mineral oil–Faecal softener and laxative.
MND–motor neuron disease
MOA–monoamine oxidase
MRL–maximum residue level
MRSA–methicillin-resistant *Staphylococcus aureus*
MSSA–methicillin-sensitive *Staphylococcus aureus*
MTHFR–methylenetetrahydrofolate reductase
Mucilage–Sticky mixture of carbohydrates produced by plant cell activity. Herbs with a high mucilaginous content are often used as demulcents (e.g. *Ulmus fulvus* (slippery elm), *Althea officinalis* (marshmallow)).
Mucolytic–Substance that dissolves or destroys mucus.
Myocardial infarction (MI)–Necrosis (death) of a portion of the heart muscle; also called a heart attack.
NAD–nicotinamide adenine dinucleotide
NADPH–nicotinamide adenine dinucleotide phosphate
Narrow therapeutic index (NTI)–The dose required to produce a toxic effect in 50% of test animals (TD_{50}) is close to the dose required to produce an effective therapeutic response in 50% of test animals (ED_{50}); NTI drugs are particularly susceptible to adverse interactions (e.g. digoxin).
Nervine–Substance that exerts a relaxant effect; described as nourishing and strengthening the nervous system.
Neurotransmitter–Chemical that acts as a messenger, enabling transmission of nerve impulses across synapses and neuromuscular junctions. The most important are acetylcholine, catecholamines (noradrenaline, adrenaline and dopamine), serotonin, some amino acids and neuro-active peptides.
NK–natural killer [cell]
NO–nitric oxide
NSAID–non-steroidal anti-inflammatory drug
Nutritive–Substance that contains numerous nutrients such as vitamins, minerals, carbohydrates and fats.
NYHA–New York Heart Association [classification]
OA–osteoarthritis
OCP–oral contraceptive pill
OS–oxygen species
OTC–over-the-counter
Oxytocic–Substance that exerts similar effects to oxytocin (i.e. stimulates smooth muscle, usually of the uterus, to contract).
P-glycoprotein (P-gp)–P-gp is a transport protein found on the surface of hepatocytes, renal tubular epithelial cells, epithelial cells in the intestine, and placenta and capillary epithelial cells in the brain. It has a counter-transport activity (i.e. can transport medicines from the blood back into the gastrointestinal tract, thereby reducing bioavailability).
PCOS–polycystic ovaries syndrome
PEF–peak expiratory flow
Peri-operative–Pertaining to the time of surgery.
PG–prostaglandin
Pharmacodynamics–Study of the effects of drugs on living organisms.
Pharmacokinetics–Study of the actions of drugs within the body (i.e. absorption, distribution, metabolism and excretion, onset of action and duration of effect).
Phytochemical–Naturally occurring chemical found in a plant.
Phytotherapy–Study and application of plant medicine; a modern term used to describe scientifically investigated and validated herbal medicine.
Placebo–Harmless inactive substance that does not contain an active medicine; used in clinical studies for comparison with medicines suspected of exerting a clinical effect to determine whether in fact a significant response does occur.
PMS–premenstrual syndrome

PO–per os (oral)
Polypharmacy–Use of many medicines by a patient with one or more health conditions.
Polysaccharide–Carbohydrate polymer formed from three or more sugar molecules.
Postprandial–After a meal.
Poultice–Paste made from crushed fresh plant, either mixed with oil or alcohol or simply made in water and applied to the parts of the body.
PPI–proton-pump inhibitors
ppm–parts per million
Prospective study–Study designed to determine the relationship between a condition and a characteristic shared by some members of a group. Usually the population selected is healthy at the beginning of the study and is observed over a period of time for the development of certain conditions in the different subgroups (e.g. smokers and non-smokers).
PTH–parathyroid hormone
PUFA–polyunsaturated fatty acid
PUVA–psoralen ultraviolet A
QOL–quality of life
RA–rheumatoid arthritis
RAST–radioallergosorbent test
RCT–randomised controlled trial
RDA–recommended daily allowance
RDI–recommended daily intake
Resin–Excreted from specialised cells or ducts in plants, this consists of a mixture of essential oils and polymerised terpenes; usually insoluble in water. Well-known examples include frankincense (*Boswellia sacra*) and myrrh (*Commiphora molmol*), both of the Burseraceae family
Restorative–Restores or renews a person's state of health or consciousness to normal.
Rhizome–Root; underground fleshy stem that grows horizontally and acts as food storage for the plant.
Risk factor–Factor that increases a person's susceptibility to an unwanted, unpleasant or unhealthy event or disease.
Root–Fleshy or woody, usually underground, part of a plant; may be fibrous (e.g. *Urtica dioica* or *U. radix* of the Urticaceae family, stinging nettle), solid (e.g. *Glycyrrhiza glabra* of the Leguminosae family, licorice) or fleshy (e.g. *Harpagophytum procumbens* of the Pedaliaceae family, devil's claw).
ROS–reactive oxygen species
Salicylate–Substance that contains or is derived from salicylic acid.
Saponin–Vast group of glycosides that occur in many plants; dissolve in water and form a soapy solution when shaken; used in demulcents.
SBP–systolic blood pressure
SC–subcutaneous
Seeds–Contained in the fruit and used medicinally (e.g. fennel seed, *Foeniculum vulgare*: Apiaceae).
SLE–systemic lupus erythematosus
SSRI–selective serotonin reuptake inhibitor
SVCT–sodium vitamin C co-transporters
Synergistic–Several components acting or working together in a coordinated manner to produce an effect greater than that of the sum of the individual effects.
Tannin–Substance that forms a precipitate with proteins, nitrogenous bases, polysaccharides and some alkaloids and glycosides (e.g. *Camellia sinensis*, the herb commonly used to make 'tea', is a rich source of tannins).
TCM–traditional Chinese medicine
TGA–Therapeutic Goods Administration (Australia)
Th–T helper cell
Therapeutic index–Measure of the safety of a medicine based upon the dose required to produce a toxic effect in 50% of test animals (TD_{50}) divided by the dose required to produce an effective therapeutic response in 50% of test animals (ED_{50}); i.e. $TI = TD_{50}/ED_{50}$.
Thin layer chromatography–Analytical method using glass or aluminium plates precoated with the sorbent (e.g. silica gel) to separate a compound mixture according to the polarity of its components.
Tincture–Hydro-ethanolic extraction of crude herbal material; usually extracted in the ratio of 1:5 (1 part herb to 5 parts solvent). Glyceride tinctures may be prepared by using glycerol rather than alcohol.
TNF–tumour necrosis factor
TPN–total parenteral nutrition
TSH–thyroid stimulating hormone
URTI–upper respiratory tract infection
UTI–urinary tract infection
UV–ultraviolet
VAS–visual analogue scale
VDR–vitamin D receptors
Vitamin–Organic compound essential to life. With few exceptions, vitamins cannot be synthesised in the body and must be obtained from the diet.
VLDL–very low-density lipoprotein
WOMAC–Western Ontario and McMasters University Osteoarthritis Index
WSR–whole systems research

APPENDIX 2

HERB/NUTRIENT–DRUG INTERACTIONS

NOTES

Assumptions

The following assumptions were made when collating and assessing information for this table:

- Information has been compiled from the monographs included in this book.
- The clinical significance of many interactions is still unknown because controlled trials are lacking in most cases. In these instances, interactions are based on evidence of pharmacological activity and case reports, and have a sound theoretical basis, although remain to be tested.
- All information refers to oral dose forms unless otherwise specified.
- Information is correct at the time of writing; however, because of the ever-expanding knowledge base developing in this area, new research is constantly being published.
- The interaction table is provided as a guide only and should not replace the use of professional judgment. It has been developed to assist clinicians when advising patients.

Using this guide in practice

- Refer to Chapter 8 (Interactions with herbal and natural medicines) for background information.
- Commonly used prescription and over-the-counter medications are organised by therapeutic class and subclass and are listed alphabetically.
- Common names have been used when referring to herbs.
- Refer to the original monograph for more information about a particular substance.

Recommendations

Avoid — There may be insufficient information available to be able to advise using the two substances safely together, so avoid until more is known. The drug may have a narrow therapeutic index and there is sufficient evidence to suggest that the interaction may be clinically significant. Consider an alternative treatment that is unlikely to produce an undesirable interaction.

Avoid use unless under medical supervision — Harmful effects of the potential interaction can be avoided if doses are altered appropriately under professional supervision or the patient is closely monitored. Some of these interactions can be manipulated to the advantage of the patient. Changes to the dosage regimen may be required for safe combined use.

Exercise caution — The possibility exists of an interaction that may change effects clinically; be aware and monitor. It is prudent to tell patients to be aware and seek advice if they are concerned.

Observe — Interaction may not be clinically significant at the usual recommended doses and may be theoretical; however, the clinician should be alert to the possibility of an interaction.

Beneficial interaction possible — Prescribing the interacting substance may improve clinical outcomes; for example, reducing drug requirements, complementing drug effects, reducing drug side effects, counteracting nutritional deficiencies caused by drugs, alleviating drug withdrawal symptoms and enhancing patient wellbeing.

Key to the table by herb/supplement

Drug	Herb or supplement	Potential outcome	Recommendation	Evidence/Comments
ALLERGIC DISORDERS				
Antihistamines				
Antihistamines and mast-cell-stabilising drugs	Albizia	Has additive effects.	Beneficial interaction possible.	Both in vitro and in vivo tests have reported significant mast-cell-stabilisation effects similar to those of cromoglycate — clinical significance unknown.
	Baical skullcap	Additive effects.	Beneficial interaction possible.	Luteolin and baicalein have been shown to inhibit IgE antibody-mediated immediate- and late-phase allergic reactions in mice — clinical significance unknown.
	Perilla	Additive effects.	Observe — drug dose may need modification.	Perilla seed extract has been shown to inhibit histamine release from mast cells in a dose-dependent manner — clinical significance unknown
ANALGESIA				
Narcotic analgesics				
Codeine	Adhatoda	Additive effects.	Beneficial interaction possible.	Theoretically will increase antitussive effects of drug.
	Kava kava	Additive effects.	Exercise caution.	Increased CNS depression theoretically possible.
Morphine	Kava kava	Additive effects.	Exercise caution — may be beneficial under professional supervision.	Increased CNS depression theoretically possible.
	Tyrosine	Additive effects.	Observe — potential beneficial interaction under professional supervision.	Tyrosine potentiates morphine-induced analgesia by 154% in mice.
	Withania	Reduced morphine tolerance/dependence.	Beneficial interaction possible with professional supervision.	In animal studies, repeated administration of withania (100 mg/kg) inhibited morphine tolerance and dependence, so it is sometimes used in opiate withdrawal.
Simple analgesics and antipyretics				
Simple analgesics and antipyretics	Meadowsweet	Additive effects.	Observe — beneficial interaction possible.	Additive anti-inflammatory and analgesic effects theoretically possible.
	Vitamin E	Additive effects.	Beneficial interaction possible. Drug dosage may require modification.	Vitamin E may enhance the pain-modifying effects of drug in RA.
	Willowbark	Additive effects.	Observe — beneficial interaction possible.	Additive anti-inflammatory and analgesic effects theoretically possible.

Continued

Drug	Herb or supplement	Potential outcome	Recommendation	Evidence/Comments
Aspirin	Andrographis	Increased bruising and bleeding.	Observe.	Herb inhibits platelet aggregation, observed in animal and clinical studies.
	Bilberry	Increased bruising and bleeding.	Exercise caution with high-dose (> 170 mg) anthocyanadins unless under medical supervision.	Dose is extremely high and not relevant to clinical practice.
	Evening primrose oil	Increased bruising and bleeding.	Observe, although beneficial interaction possible.	Theoretically concomitant use may enhance anti-inflammatory and antiplatelet effects — clinical significance unknown.
	Feverfew	Increased bruising and bleeding.	Interaction unlikely but observe.	Feverfew inhibits platelet aggregation in vitro and in vivo, no effects were seen in clinical study; however, contradictory evidence exists.
	Fish oils	Additive effects.	Observe — beneficial interaction possible.	No haemorrhagic effects were seen in a clinical study — theoretical concern only if increased bruising or bleeding. Pharmacological activity of fish oils may have benefits for some patients taking aspirin for CVD prevention or for its anti-inflammatory properties.
	Garlic	Increased bruising and bleeding.	Interaction unlikely at usual doses. Observe when using higher doses (> 7 g).	Theoretically, a pharmacodynamic interaction is possible when using garlic at high doses (> 7 g) in excess of usual dietary amounts; however, results from clinical studies cast doubt on this proposition.
	Ginger	Increased bruising and bleeding.	Interaction unlikely at usual doses. Exercise caution at high dose (> 10 g) unless under professional supervision.	Inhibits platelet aggregation at very high doses — dietary intake appears safe.
	Ginkgo biloba	Increased bruising and bleeding.	Interaction unlikely.	Pharmacodynamic interaction theoretically possible because of platelet-activating-factor inhibitor activity; however, clinical trials show no significant change to bleeding or platelet activity, so interaction unlikely to be significant.
	Grapeseed extract	Increased bruising and bleeding.	Observe.	Theoretically may enhance antiplatelet activity and anti-inflammatory activity of aspirin and may increase risk of bleeding.
	Guarana	Increased bruising and bleeding.	Observe.	Theoretically possible as in vitro and in vivo research has identified antiplatelet activity — clinical significance unknown.
	Meadowsweet	Increased bruising and bleeding.	Observe — beneficial interaction possible.	Theoretically may enhance anti-inflammatory and antiplatelet effects.
	Myrrh	Increased bruising and bleeding.	Observe with myrrh preparations. Exercise caution with guggul preparations.	Guggul inhibited platelet aggregation in vitro and in a clinical study, so concurrent use may theoretically increase the risk of bleeding — implications for *Commiphora molmol* use unclear.

Drug	Herb or supplement	Potential outcome	Recommendation	Evidence/Comments
	Policosanol	Increased bruising and bleeding.	Observe.	Doses > 10 mg/day may inhibit platelet aggregation.
	Turmeric	Increased bruising and bleeding.	Observe with concentrated extracts.	Curcumin inhibits platelet aggregation in vitro and in vivo — clinical significance is unclear and likely to be dose dependent.
	Vitamin C	Decreased vitamin C effects.	Observe.	Aspirin may interfere with both absorption and cellular uptake mechanisms for vitamin C, thereby increasing vitamin C requirements, as observed in animal and human studies. Increased vitamin C intake may be required with long-term therapy.
	Willowbark	Increased bruising and bleeding.	Exercise caution with high dose (> 240 mg/day).	Theoretically may enhance anti-inflammatory and antiplatelet effects. Although a clinical study found that consumption of salicin 240 mg/day produced minimal effects on platelet aggregation, higher doses may have a significant effect.
Paracetamol	Andrographis	Reduced side effects.	Beneficial interaction possible	Andrographis may exert hepatoprotective activity against liver damage induced by paracetamol.
	Garlic	Reduced side effects.	Beneficial interaction possible.	Garlic may exert hepatoprotective activity against liver damage induced by paracetamol.
	Quercetin	Reduced side effects.	Beneficial interaction possible.	Quercetin may exert hepatoprotective activity against liver damage induced by paracetamol.
	St Mary's thistle	Reduced side effects.	Beneficial interaction possible under professional supervision.	St Mary's thistle may exert hepatoprotective activity against liver damage induced by paracetamol.
	SAMe	Reduced side effects.	Beneficial interaction possible.	SAMe may exert hepatoprotective activity against liver damage induced by paracetamol.
	Schisandra	Reduced side effects.	Beneficial interaction possible.	Schisandra may exert hepatoprotective activity against liver damage induced by paracetamol.
CARDIOVASCULAR SYSTEM				
Anti-angina agents				
Nitroglycerin/glyceryl trinitrate (e.g. anginine)	Arginine	Additive hypotensive effects.	Caution.	Theoretically, additive vasodilation and hypotensive effects may occur.
	Vitamin E	Prevention of drug tolerance.	Beneficial interaction possible.	Oral vitamin E prevented nitrate tolerance when given concurrently with transdermal nitroglycerin (10 mg/24 h) according to one randomised placebo-controlled study

Continued

Drug	Herb or supplement	Potential outcome	Recommendation	Evidence/Comments
Anti-impotence				
Phosphodiesterase-5 Inhibitor (e.g. Sildenafil)	Arginine	Additive effects.	Exercise caution.	Theoretically, additive vasodilation and hypotensive effects may occur.
Anti-arrhythmic agents				
	Astragalus	Additive effects.	Observe.	Additive effects are theoretically possible with IV administration of astragalus, based on positive inotropic activity identified in clinical studies; the clinical significance of these findings for oral dose forms is unknown.
	Devil's claw	Additive effects.	Observe.	Devil's claw has demonstrated anti-arrhythmic activity, but interaction is theoretical and clinical significance is unclear.
	Hawthorn	Additive effects.	Observe.	Hawthorn has demonstrated anti-arrhythmic activity in vitro and in vivo, but interaction is theoretical and clinical significance is unclear.
	Magnesium	Additive effects.	Observe.	High-dose oral magnesium has demonstrated anti-arrhythmic activity according to one clinical trial.
Amiodarone	Vitamin B_6 (pyridoxine)	Increased drug side effects.	Exercise caution.	Vitamin B_6 may increase risk of drug-induced photosensitivity.
Anticoagulants, antiplatelets Monitor bleeding time and signs and symptoms of excessive bleeding				
Anticoagulants (e.g. warfarin)	Andrographis	Increased bruising and bleeding.	Exercise caution — monitor bleeding time.	Andrographolide and other constituents of andrographis are clinically confirmed to inhibit platelet-activating-factor-induced platelet aggregation.
	Baical skullcap	Increased risk of bruising and bleeding.	Exercise caution.	Baical flavonoids have been shown to inhibit platelet aggregation in vitro — clinical significance unknown.
	L-Carnitine	Increased bruising and bleeding.	Observe.	According to one case report, L-carnitine 1 g/day may potentiate the anticoagulant effects of acenocoumarol. Further investigation required to confirm interaction.
	Celery	Increased bruising and bleeding.	Observe with high dose extracts.	Although celery contains naturally occurring coumarins, interaction is unlikely.
	Chamomile	Increased bruising and bleeding.	Observe.	According to one case report, internal haemorrhage occurred in elderly patient taking warfarin and topical and oral chamomile preparations. Further investigation required to confirm interaction.

Drug	Herb or supplement	Potential outcome	Recommendation	Evidence/Comments
	Chondroitin	Increased bruising and bleeding.	Observe.	Theoretical risk; not observed in clinical trials.
	Coenzyme Q10	Reduced drug effects.	Interaction unlikely with standard doses. Observe patients taking high doses.	A double-blind crossover study found that oral CoQ10 100 mg/day had no significant effect on INR or warfarin levels; however, in vivo tests using 10 mg/kg/day CoQ10 decreased serum concentrations of warfarin by increasing drug metabolism.
	Cranberry	Increased bruising and bleeding.	Exercise caution — due to potential seriousness of interaction.	Clinical investigations are conflicting. However a recent study suggests a pharmocodynamic interaction is likely. Monitor INR closely.
	Devil's claw	Increased bruising and bleeding.	Observe until clinical studies can confirm interaction.	Case reports suggest possible anticoagulant activity but most are inconclusive. Further investigation required to confirm interaction.
	Dong quai	Increased bruising and bleeding.	Observe with oral supplements.	A controlled trial using an IV preparation of dong quai found that it prolonged prothrombin times, but it is unknown whether this effect occurs with oral dose forms.
	Evening primrose oil	Increased bruising and bleeding.	Exercise caution — monitor bleeding time, signs and symptoms.	Gamma-linoleic acid in evening primrose oil affects prostaglandin synthesis, leading to inhibition of platelet aggregation — clinical significance is unknown.
	Fenugreek	Increased bruising and bleeding.	Interaction unlikely.	While it contains naturally occurring coumarins, a placebo-controlled study found no effect on platelet aggregation, fibrinogen or fibrinolytic activity.
	Feverfew	Increased bruising and bleeding.	Interaction unlikely. Observe.	Although feverfew inhibits platelet aggregation in vitro and in vivo, no effects were seen in a clinical study.
	Fish oils	Increased bruising and bleeding.	Interaction unlikely at usual therapeutic doses. Exercise caution with very high doses (> 12 g) unless under medical supervision.	A review of clinical studies concluded there was no clinically significant effect on bleeding with usual therapeutic doses. According to one clinical study, bleeding time may be increased at high doses of 12 g/day.
	Garlic	Increased bruising and bleeding.	Interaction unlikely at usual dietary intake. Exercise caution with use of high dose (> 7 g) supplements.	Theoretically, a pharmacodynamic interaction is possible when using garlic at high doses (> 7 g) in excess of usual dietary amounts; however, results from clinical studies cast doubt on this proposition.
	Ginger	Increased bruising and bleeding.	Observe at usual therapeutic doses. Exercise caution at high dose (> 10 g).	Inhibits platelet aggregation at high doses.
	Ginkgo biloba	Increased bruising and bleeding.	Interaction unlikely based on clinical trials. Observe high risk patients — due to potential seriousness of interaction.	Theoretically ginkgo may increase bleeding and there have been several case reports of haemorrhage; however, evidence from clinical studies does not support this. Ginkgo has no effect on pharmacokinetics, pharmacodynamics or clinical effects of warfarin. This is supported by a recent systematic review.

Continued

Drug	Herb or supplement	Potential outcome	Recommendation	Evidence/Comments
	Ginseng — Korean	Possibly increased bruising and bleeding.	Observe.	Two case reports have indicated ginseng reduced antithrombotic effects of warfarin. In vitro and in vivo ginseng has demonstrated inhibition of platelet aggregation; however, a recent open-label study found no effect of ginseng on warfarin in healthy males.
	Ginseng — Siberian	Increased bruising and bleeding.	Observe.	In vivo study demonstrated that an isolated constituent in Siberian ginseng has anticoagulant activity and a clinical trial found a reduction in blood coagulation induced by intensive training in athletes — whether these effects also occur in non-athletes is unknown. A recent combination study of Siberian ginseng, andrographis and warfarin produced no significant effects on drug pharmacokinetics and pharmacodynamics.
	Glucosamine		Exercise caution until interaction can be confirmed.	Case reports suggest a possible interaction with warfarin.
	Goji	Increased bruising and bleeding.	Exercise caution until interaction confirmed clinically.	Two case reports of interaction between goji and warfarin producing altered INR. Further investigation required to confirm interaction.
	Grapeseed extract	Increased bruising and bleeding.	Exercise caution until interaction confirmed clinically.	Inhibits platelet aggregation in vitro and ex vivo — clinical significance unknown.
	Green tea	Reduced drug effects.	Exercise caution with high doses.	A case report of excessive intake (2.25–4.5 L green tea daily) was reported to inhibit warfarin activity and decrease INR. Further investigation required to confirm interaction.
	Guarana	Increased bruising and bleeding.	Exercise caution until interaction confirmed clinically.	In vitro and in vivo research has identified antiplatelet activity — clinical significance unknown.
	Horseradish	Increased bruising and bleeding risk.	Interaction unlikely.	Although it contains coumarins, interaction unlikely.
	Licorice	Increased bruising and bleeding.	Exercise caution until interaction confirmed clinically.	Isoliquiritigenin inhibits platelet aggregation, and glycyrrhizin inhibits prothrombin, according to in vitro and in vivo tests — clinical significance unknown.
	Meadowsweet	Increased bruising and bleeding.	Observe until interaction confirmed clinically.	In vitro tests have indicated anticoagulant activity — clinical significance unknown.
	Myrrh	Increased bruising and bleeding.	Observe with myrrh preparations. Exercise caution with guggul preparations.	Guggul inhibited platelet aggregation in vitro and in a clinical study, so concurrent use may theoretically increase the risk of bleeding — implications for *Commiphora molmol* use unclear.
	Policosanol	Increased bruising and bleeding.	Exercise caution with doses > 10 mg daily.	Current evidence is contradictory, as one study failed to detect an interaction between policosanol and warfarin, but others have found that doses > 10 mg/day may inhibit platelet aggregation.

Drug	Herb or supplement	Potential outcome	Recommendation	Evidence/Comments
	Psyllium	Decreased drug absorption.	Separate doses by at least 1 hour.	
	Red clover	Increased bruising and bleeding.	Interaction unlikely.	Theoretically, coumarin content could exert anticoagulant activity; however, dicoumarol produced by microorganisms in poorly dried sweet clover has established anticoagulant effects. Interaction unlikely from extracts prepared from properly dried red clover.
	Rosemary	Increased bruising and bleeding.	Exercise caution with concentrated extracts until interaction confirmed clinically.	Rosemary demonstrates antithrombotic activity in vitro and in vivo — clinical significance unknown.
	St John's wort (unlikely to relate to low-hyperforin-containing products)	Decreased drug effects.	Exercise caution — monitor for signs of reduced drug effectiveness and adjust dose if necessary. Prothrombin time or INR should be closely monitored with addition or withdrawal of St John's wort.	Metabolism of warfarin is chiefly by CYP2C9, and a minor metabolic pathway is CYP3A4, so theoretically it may interact with St John's wort. A clinical study found no change to INR or platelet aggregation (Jiang et al 2004), but there are case reports suggesting St John's wort may lower the INR.
	Slippery elm	Decreased drug absorption.	Separate doses by at least 2 hours.	Theoretical interaction — clinical significance unknown.
	Turmeric	Increased bruising and bleeding.	Exercise caution with concentrated extracts until interaction confirmed clinically.	Curcumin inhibits platelet aggregation in vitro and in vivo — concomitant use with high dose turmeric may theoretically increase risk of bleeding.
	Vitamin E	Increased bruising and bleeding.	Exercise caution with high-dose supplements (> 1000 IU daily). Until clinical significance can be established, prothrombin time or INR should be closely monitored with addition or withdrawal of high-dose vitamin E supplements.	Clinical studies have produced conflicting results: several found no effects of platelet aggregation or coagulation, although others found an increased bleeding risk. Clinical study of 1200 IU/d for 28 days had no effects on platelet aggregation; another of 900 IU/d for 12 weeks did not alter coagulation activity. Alternatively 50 mg/d increased gingival bleeding. Overall, it appears people with reduced levels of vitamin K may be more susceptible to the effects of vitamin E potentiating warfarin activity.
	Willow bark	Increased bruising and bleeding.	Exercise caution with high dose (> 240 mg/day).	Theoretically, may enhance anti-inflammatory and antiplatelet effects. Although a clinical study found that consumption of salicin 240 mg/day produced minimal effects on platelet aggregation, higher doses may have a significant effect.
Antiplatelet drugs (e.g. aspirin)	Andrographis	Increased bruising and bleeding.	Observe.	Herb inhibits platelet aggregation, observed in animal and clinical studies.

Continued

Drug	Herb or supplement	Potential outcome	Recommendation	Evidence/Comments
	Bilberry	Increased bruising and bleeding.	Exercise caution with high-dose (> 170 mg) anthocyanadins unless under medical supervision.	Dose is extremely high and not relevant to clinical practice.
	Evening primrose oil	Increased bruising and bleeding.	Observe, although beneficial interaction possible.	Theoretically, concomitant use may enhance anti-inflammatory and antiplatelet effects — clinical significance unknown.
	Feverfew	Increased bruising and bleeding.	Observe.	Feverfew inhibits platelet aggregation in vitro and in vivo; no effects were seen in clinical study; however, contradictory evidence exists.
	Fish oils	Additive effects.	Observe — beneficial interaction possible.	No haemorrhagic effects were seen in a clinical study — theoretical concern. Pharmacological activity of fish oils may have benefits for some patients taking aspirin for CVD prevention or for its anti-inflammatory properties.
	Garlic	Increased bruising and bleeding.	Interaction unlikely.	Theoretically, may enhance platelet aggregation. Recent clinical investigation found garlic had no effect on platelet function.
	Ginger	Increased bruising and bleeding.	Interaction unlikely at standard intake. Exercise caution at high dose (> 10 g) unless under professional supervision.	Inhibits platelet aggregation at very high doses.
	Ginkgo biloba	Increased bruising and bleeding.	Interaction unlikely.	Theoretically possible because of platelet-activating-factor inhibitor activity. There are rare case reports of haemorrhage and haematoma; however, clinical trials show no significant change to bleeding or platelet activity. This is confirmed in a recent systematic review.
	Grapeseed extract	Increased bruising and bleeding.	Observe.	Theoretically, may enhance antiplatelet activity.
	Guarana	Increased bruising and bleeding.	Observe.	Theoretically possible, as in vitro and in vivo research has identified antiplatelet activity — clinical significance unknown.
	Meadowsweet	Increased bruising and bleeding.	Observe — beneficial interaction possible.	Theoretically may enhance anti-inflammatory and antiplatelet effects.
	Myrrh	Increased bruising and bleeding.	Observe with myrrh preparations. Exercise caution with guggul preparations.	Guggul inhibited platelet aggregation in vitro and in a clinical study, so concurrent use may theoretically increase the risk of bleeding — implications for *Commiphora molmol* use unclear.
	Policosanol	Increased bruising and bleeding.	Observe.	Doses > 10 mg/day may inhibit platelet aggregation.
	Turmeric	Increased bruising and bleeding.	Observe with concentrated extracts.	Curcumin inhibits platelet aggregation in vitro and in vivo — clinical significance is unclear and likely to be dose dependent.

Drug	Herb or supplement	Potential outcome	Recommendation	Evidence/Comments
	Vitamin C	Decreased vitamin C effects.	Observe.	Aspirin may interfere with both absorption and cellular uptake mechanisms for vitamin C, thereby increasing vitamin C requirements, as observed in animal and human studies. Increased vitamin C intake may be required with long-term therapy.
	Willow bark	Increased bruising and bleeding.	Interaction unlikely at usual doses. Exercise caution with high dose (> 240 mg/day)	Theoretically, may enhance anti-inflammatory and antiplatelet effects. Although a clinical study found that consumption of salicin 240 mg/day produced minimal effects on platelet aggregation, higher doses may have a significant effect.
Antihypertensive agents				
Antihypertensive drugs	Arginine	Additive hypotensive effects.	Exercise caution.	Theoretical concern.
	Essential fatty acids — omega-3 and omega-6	Increased drug effects.	Observe — beneficial interaction possible.	Both omega-3 and omega-6 fatty acids exhibit mild antihypertensive activity.
	Evening primrose oil	Additive effects.	Observe — monitor drug requirements (interaction may be beneficial).	Evening primrose oil has been shown to enhance the effects of several antihypertensive drugs, including dihydralazine, clonidine and captopril in rats under experimental conditions.
	Garlic	Additive effects.	Observe — beneficial interaction possible.	Clinical trials have shown garlic to reduce blood pressure, which may lead to reduced drug requirements.
	Hawthorn	Additive effects.	Observe — beneficial interaction possible.	Mild antihypertensive activity has been reported with long-term use of hawthorn, which may lead to reduced drug requirements.
	Licorice	Reduced drug effect.	Exercise caution — monitor blood pressure when high-dose licorice preparations are taken for more than 2 weeks.	High-dose glycyrrhizin taken long-term can lead to increased blood pressure.
	Oats (oat-based cereals)	Additive effects.	Observe — monitor drug requirements (interaction may be beneficial).	A clinical trial has shown that ingestion of oat-based cereals decreased blood pressure in 73% of hypertensive patients and reduced drug requirements. Patients taking oats, oat milk and oat bran should be monitored.
	Olive leaf and olive oil	Additive effects.	Possible beneficial interaction possible under professional supervision.	Theoretical, as hypotensive effects have been observed with olive oil and olive leaf extracts.
	Stinging nettle	Additive effects.	Observe.	Additive effects are theoretically possible.

Continued

Drug	Herb or supplement	Potential outcome	Recommendation	Evidence/Comments
Hydralazine (e.g. Apresoline, Alphapress)	Coenzyme Q10	Reduced CoQ10 serum levels.	Beneficial interaction possible.	Increased CoQ10 intake may be required with long-term therapy.
	Vitamin B_6 (pyridoxine)	Reduced vitamin B_6 absorption.	Separate doses by at least 2 hours.	A clinical trial has shown that the drug may induce B_6 deficiency, so increased intake may be required with long-term therapy.
Methyldopa (e.g. Aldomet)	Coenzyme Q10	Reduced CoQ10 serum levels.	Beneficial interaction possible.	Increased CoQ10 intake may be required with long-term therapy.
ACE inhibitors (e.g. captopril, enalapril)	Iron	Reduced drug effect.	Separate doses by at least 2 hours.	Reduced absorption of ACE inhibitors. A small clinical trial found that concomitant iron administration reduced area-under-the-curve plasma levels of unconjugated captopril by 37%.
	Zinc	Reduced zinc levels.	Monitor for zinc efficacy and zinc status.	These drugs increase urinary excretion of zinc. Increased zinc intake may be required with long-term therapy.
Verapamil	St John's wort	Reduces drug levels via increased metabolism.	Monitor and adjust dose as necessary.	Decreases drug serum levels via CYP induction.
Beta-adrenergic-blocking agents	Coenzyme Q10	Reduced CoQ10 serum levels.	Beneficial interaction possible.	Increased CoQ10 intake may be required with long-term therapy.
	Calcium	Reduced drug effects.	Separate doses by at least 2 hours.	Simultaneous use can reduce both agents. Separate doses by 2 hours.
Propranolol	Myrrh	Reduced drug effect.	Observe.	A clinical trial has shown that guggulipid reduces bioavailability of propranolol. It is uncertain what implications this has for use of *Commiphora molmol.*
	Vitamin E	Reduced drug effect.	Observe.	According to in vitro research, vitamin E inhibits drug uptake in human cultured fibroblasts — clinical significance unknown.
Calcium-channel blockers (e.g. verapamil)	Calcium	Reduced drug effect.	Avoid high-dose supplements unless under medical supervision.	Calcium may reduce antihypertensive effect of drug.
	Magnesium	Additive effects.	Observe — monitor drug requirements (interaction may be beneficial).	A meta-analysis of 20 randomised trials showed that magnesium has a modest antihypertensive activity and may enhance the activity of calcium-channel blockers.
	Vitamin D	Reduced drug effect.	Exercise caution unless under medical supervision.	Vitamin D may reduce effectiveness of these drugs.
Felodipine	Peppermint oil	Increased drug effects.	Exercise caution.	Peppermint oil has been shown to increase the oral bioavailability of felodipine in animal studies.

Drug	Herb or supplement	Potential outcome	Recommendation	Evidence/Comments
Nifedipine	Ginseng — Korean	Increased drug effects.	Exercise caution.	
	St John's wort	Reduced drug effect.	Monitor for signs of reduced drug effectiveness — adjust dose where necessary.	St John's wort has been shown to induce nifedipine metabolism.
Diltiazem	Myrrh	Reduced drug effect.	Observe.	A clinical trial has shown that guggulipid reduces bioavailability of diltiazem. It is uncertain what implications this has for use of *Commiphora molmol*.
	Quercetin	Increased drug effects.	Exercise caution under professional supervision; drug dose may need adjustment.	Increased drug bioavailability observed in vivo — clinical significance unknown.
Antimigraine preparations				
Antimigraine preparations	Coenzyme Q10	Additive effects.	Beneficial interaction possible.	CoQ10 demonstrated migraine-prevention activity in a clinical study.
	Feverfew	Additive effects.	Beneficial interaction possible.	Feverfew demonstrated migraine-prevention activity in several clinical studies.
	Vitamin B_2 (riboflavin)	Additive effects.	Beneficial interaction possible.	Vitamin B_2 has demonstrated migraine-prevention activity in several clinical studies.
Clonidine (e.g. Catapres)	Coenzyme Q10	Reduced CoQ10 serum levels.	Beneficial interaction possible.	In vivo study indicates that clonidine reduces serum CoQ10 levels. Increased CoQ10 intake may be required with long-term therapy.
Cardiac inotropic agents				
Cardiac glycosides	Calcium	Additive effects.	Exercise caution.	Concurrent use of high-dose calcium can act synergistically and may induce arrhythmias and potentiate their toxicity.
	Hawthorn	Additive effects.	Exercise caution — monitor drug requirements (interaction may be beneficial).	Theoretical interaction, as in vitro and in vivo studies indicate that hawthorn has positive inotropic activity. Small clinical study found interaction not clinically significant when digoxin 0.25 mg taken with hawthorn (WS1442) 450 mg twice daily.
	Psyllium	Reduced drug absorption.	Separate doses by at least 1 hour.	Soluble fibre may decrease the bioavailability of cardiac glycosides.

Continued

Drug	Herb or supplement	Potential outcome	Recommendation	Evidence/Comments
Digoxin (e.g. Lanoxin) Adverse effects of high-dose digoxin include: nausea, vomiting, diarrhoea, confusion, fainting, palpitations, irregular heartbeat, visual disturbances.	Aloe vera	Increased drug toxicity.	Avoid long-term use of high-dose preparations.	Long-term oral use of aloe can deplete potassium levels and reduced potassium status lowers the threshold for drug toxicity.
	Ginseng — Korean	Interferes with therapeutic drug monitoring for digoxin.	Exercise caution — drug assay may produce false positive and negative results.	There are no confirmed clinical case reports of actual interaction.
	Guarana	Increased drug toxicity.	Avoid long-term use of high-dose preparations.	Long-term guarana use can deplete potassium levels and reduced potassium status lowers the threshold for drug toxicity.
	Licorice	Increased drug toxicity.	Avoid long-term use of high-dose preparations (> 100 mg glycyrrhizin daily > 2 weeks) unless under medical supervision.	Long-term use of licorice can induce hypokalaemia, which can increase sensitivity to cardiac glycoside drugs, thereby reducing the threshold for drug toxicity. One case report exists of digitalis toxicity in an elderly man taking licorice-containing Chinese herbal laxative.
	Quercetin	Increased drug toxicity.	Avoid concurrent use owing to seriousness of interaction.	Increased drug bioavailability possible, observed by in vivo study.
	St John's wort	Reduced drug effects.	Avoid unless under medical supervision. Monitor for signs of reduced drug effectiveness and adjust dose if necessary. When St John's wort is started or ceased, monitor serum levels and alter drug dosage as required.	St John's wort induces CYP enzymes and P-glycoprotein. A clinical trial shows that St John's wort significantly decreases serum levels of drug within 10 days of concomitant use. More recently herb drug interaction was found to be clinically significant.
	Slippery elm	Decreased drug absorption.	Separate doses by at least 2 hours.	Theoretical interaction — clinical significance unknown.
	Withania	Interferes with therapeutic drug monitoring for digoxin.	Exercise caution — drug assays may be modestly altered.	

Drug	Herb or supplement	Potential outcome	Recommendation	Evidence/Comments
Diuretics				
Diuretics	Dandelion leaf	Additive effects.	Observe.	Theoretically, increased diuresis is possible — clinical significance is unknown.
	Elder	Additive effects.	Observe.	Theoretically, increased diuresis is possible with concomitant use; clinical significance is unknown.
	Green tea	Additive effects.	Observe.	Theoretically, increased diuresis possible owing to caffeine content of herb — clinical significance is unknown.
	Guarana	Additive diuretic effects but decreased hypotensive effects of drug.	Exercise caution. Monitor potassium status.	Theoretically, increased diuresis and decreased hypotensive effects are possible — clinical significance is unknown.
	Licorice	Increased potassium excretion.	Avoid long-term use unless under medical supervision. Monitor potassium status.	Potassium loss may become significant when licorice is used in high doses (> 100 mg glycyrrhizin daily) for longer than 2 weeks.
Loop diuretics	Magnesium	Increased magnesium excretion.	Monitor magnesium efficacy and status — beneficial interaction possible.	Increased magnesium intake may be required with long-term therapy.
	Stinging nettle	Additive effects.	Observe.	Theoretically, increased diuresis is possible — clinical significance is unknown.
	Vitamin B_1 (thiamin)	Reduced B_1 levels.	Monitor B_1 efficacy and status — beneficial interaction possible.	Chronic use may result in lowered vitamin status. Increase intake of vitamin B_1-containing foods or consider long-term supplementation.
	Zinc	Increased urinary zinc excretion.	Monitor zinc efficacy and status — beneficial interaction possible.	Increased zinc intake may be required with long-term therapy.
Potassium-sparing diuretics	Magnesium	Increased magnesium effects.	Observe.	
Thiazide diuretics	Calcium	Decreased urinary calcium excretion.	Observe. Monitor serum calcium and look for signs of hypercalcaemia.	
	Magnesium	Increased magnesium excretion.	Monitor magnesium efficacy and status — beneficial interaction possible.	Increased magnesium intake may be required with long-term therapy.
	Zinc	Increased urinary zinc excretion.	Monitor zinc efficacy and status — beneficial interaction possible.	Increased zinc intake may be required with long-term therapy.

Continued

Drug	Herb or supplement	Potential outcome	Recommendation	Evidence/Comments
Hydrochlorothiazide (e.g. Diclotride)	Coenzyme Q10	Reduced CoQ10 serum levels.	Beneficial interaction possible.	Increased CoQ10 intake may be required with long-term therapy.
	Vitamin B_{12} (cobalamin)	Reduces drug-induced hyper-homocysteinaemia.	Beneficial interaction possible in conjunction with folate.	Hydrochlorothiazide may increase homocysteine levels.
Hypolipidaemic agents				
Hypolipidaemic agents	Chromium	Additive effects.	Observe. Monitor drug requirements — interaction may be beneficial.	Clinical trials indicate that chromium reduces total cholesterol levels.
	Evening primrose oil	Additive effects.	Observe — interaction may be beneficial.	Several animal studies have demonstrated EPO's lipid-lowering effects — clinical significance unknown.
	Fenugreek	Additive effects.	Observe. Monitor drug requirements — interaction may be beneficial.	Clinical trials indicate that fenugreek exerts a lipid-lowering activity in diabetics with elevated lipids.
	Garlic	Additive effects.	Observe. Monitor drug requirements — interaction may be beneficial.	A meta-analysis of 13 clinical trials concluded that garlic significantly reduces total cholesterol levels — effects are described as modest.
	Myrrh	Additive effects.	Observe. Monitor drug requirements — interaction may be beneficial for guggul preparations.	Guggul has demonstrated cholesterol-lowering activity in several clinical studies.
	Oats (oat-based cereals)	Reduced drug absorption. Additive effects.	Separate doses by 2–3 hours. Beneficial interaction possible — monitor drug requirements.	Clinical trials indicate that oat-based cereals reduce total cholesterol levels. However, two case reports exist of a reduced effect of lovastatin in patients taking 50–100 g oat bran daily. This effect is probably due to the fibre content inhibiting the absorption of the drug.
	Policosanol	Additive effects.	Interaction uncertain.	Pharmacodynamic interaction previously thought possible; however, recent clinical studies cast doubt on this.
	Psyllium	Additive effects.	Beneficial interaction possible.	Recent meta-analysis confirmed the capacity of psyllium to exert a time- and dose-dependent cholesterol-lowering effect.
	Red yeast rice	Additive effects.	Observe — beneficial interaction possible. Drug dose may require modification.	Red yeast rice contains low levels of naturally occurring statins, which exert clinically significant lipid-lowering activity.

Drug	Herb or supplement	Potential outcome	Recommendation	Evidence/Comments
	Vitamin B_3 (niacin)	Additive effects.	Beneficial interaction possible — caution with sustained-release form.	Several clinical trials confirm the cholesterol-lowering activity of niacin and the safety of niacin with statins; however, the sustained-release form may be less safe.
Cholestyramine (e.g. Questran Lite, colestipol [e.g. Colestid])	Fat-soluble vitamins (A, D, E, K, beta-carotene)	Reduced vitamin absorption.	Separate doses by at least 4 hours and monitor vitamin status.	Increased dietary intake may be required or consider vitamin supplementation with long-term therapy.
	Folate	Reduced folate absorption.	Separate doses by at least 4 hours and monitor iron status.	Increased vitamin intake may be required with long-term therapy.
	Iron	Reduced iron absorption.	Separate doses by at least 4 hours and monitor iron status	Investigations have shown that cholestyramine and colestipol bind to iron citrate. Increased iron intake may be required with long-term therapy.
	Lutein and zeaxanthin	Reduced vitamin absorption.		Increased vitamin intake may be required with long-term therapy.
	Lycopene	Reduced vitamin absorption.	Separate doses by at least 2 hours and monitor vitamin status.	Drugs that reduce fat absorption may also reduce lycopene absorption. Increased vitamin intake may be required with long-term therapy.
	Vitamin D	Reduced vitamin absorption.	Separate doses by at least 1 hour prior to or 4–6 hours after drug ingestion.	Such drugs may compromise the absorption of all fat-soluble vitamins.
	Vitamin E	Reduced vitamin absorption.	Separate doses by at least 4 hours and monitor vitamin status.	Increased vitamin intake may be required with long-term therapy.
Chitosan	Vitamin C	May increase cholesterol-lowering effect.	Beneficial interaction possible.	According to preliminary animal study, concomitant use may provide additional benefit in lowering cholesterol.
Fibric-acid derivatives (e.g. gemfibrozil)	Coenzyme Q10	Reduced CoQ10 serum levels.	Beneficial interaction possible — separate doses by 4 hours.	Increased CoQ10 intake may be required with long-term therapy.
	Beta-carotene	Improved drug effects.	Beneficial interaction possible.	In clinical studies, a positive interaction was established between fibrate and beta-carotene, generating significantly increased HDL-cholesterol levels.
HMG-CoA reductase inhibitors (statins)	Carnitine	Additive effects.	Beneficial interaction.	Human studies have demonstrated the addition of L-carnitine to statin therapy lowers serum lipoprotein (a) levels in patients with type 2 diabetes.
	Coenzyme Q10	Reduced CoQ10 serum levels.	Beneficial interaction possible.	Clinical study indicates several statin drugs reduce CoQ10 levels — increased CoQ10 intake may be required with long-term therapy.
	Vitamin A	Increased vitamin A activity.	Observe.	A clinical trial has reported increased serum levels of vitamin A — clinical significance unclear.

Continued

Drug	Herb or supplement	Potential outcome	Recommendation	Evidence/Comments
	Vitamin B_3 (niacin)	Additive effects.	Beneficial interaction possible — caution with sustained-release form.	Several clinical trials confirm the cholesterol-lowering activity of niacin and the safety of niacin with statin; however, the sustained-release form may be less safe.
	Vitamin D	Increased vitamin effects.	Monitor nutrient status	Through unknown mechanisms long-term use of statins is associated with increased 25(OH)D levels — clinical significance is unknown.
Pravastatin (e.g. Pravachol)	Fish oils	Additive effects.	Beneficial interaction possible.	A clinical trial suggests improved lipid-lowering effects when used concurrently. In particular, fish oils will lower triglycerides.
Simvastatin (e.g. Lipex, Zocor)	Peppermint oil	Additive effects.	Observe. Monitor drug requirements — interaction may be beneficial.	Peppermint oil has been shown to increase the oral bioavailability of simvastatin in animal studies — clinical significance unknown.
	St John's wort	Reduced drug effects.	Monitor for signs of reduced drug effectiveness and adjust the dose if necessary.	St John's wort increases metabolism of simvastatin (interaction not expected with pravastatin).
CENTRAL NERVOUS SYSTEM				
Anticonvulsants				
Anticonvulsants	L-Carnitine	Reduced side effects.	Beneficial interaction possible.	L-Carnitine deficiency may cause or potentiate valproic acid toxicity, and supplementation is known to reduce the toxicity of valproate as well as symptoms of fatigue — concurrent use is recommended, as a beneficial interaction is possible.
	Folate	Reduced side effects.	Monitor for drug effectiveness. Beneficial interaction possible.	Requires close supervision to ensure that drug efficacy is not substantially reduced.
	Ginkgo biloba	Reduced drug effects.	Observe.	Based on case reports — further investigation required.
	Psyllium	Reduced drug absorption.	Separate doses by 1–1.5 hours before or after drug.	Absorption of drug concomitantly with psyllium may be delayed.
	St John's wort	Reduced drug effects.	Avoid unless under medical supervision to alter doses appropriately. When St John's wort is started or ceased, monitor serum levels and alter drug dosage as required.	St John's wort may increase drug metabolism, resulting in reduced drug efficacy.

Drug	Herb or supplement	Potential outcome	Recommendation	Evidence/Comments
Carbamazepine (e.g. Tegretol) NTI: signs of overdose include CNS and respiratory depression, hypotension, vomiting, fluid retention.	St Mary's thistle	Increased drug effects.	Exercise caution — monitor drug requirements.	May reduce metabolism of drug resulting in increased serum levels and adverse effects (difficult to evaluate evidence).
	Vitamin B_{12} (cobalamin)	Decreased B_{12} levels.	Observe for signs and symptoms of B_{12} deficiency. Beneficial interaction possible.	In studies with children, long-term carbamazepine use led to a decrease in vitamin B_{12} levels. Increased intake may be required with long-term therapy.
Phenobarbitone	Celery	Prolonged action.	Exercise caution.	Celery juice has been found to prolong the action of phenobarbitone in rats — clinical significance unknown.
	Withania	Increased sedation.	Observe, although beneficial interaction possible under professional supervision.	
Phenobarbitone and phenytoin	Kava kava	Increased sedation.	Exercise caution.	
	St John's wort	Decreased drug effects (increased drug metabolism).	Avoid — monitor drug requirements. When St John's wort is started or ceased, monitor serum levels and alter drug dosage as required.	St John's wort may increase drug metabolism, resulting in reduced drug efficacy.
	Vitamin B_{12} (cobalamin)	Increased serum B_{12} levels.	Observe.	One clinical study reported that combined long-term use of phenobarbitone and phenytoin resulted in significantly increased serum B_{12} levels — clinical significance unknown.
Phenytoin	Vitamin B_6 (pyridoxine)	Reduced drug effects.	Exercise caution — monitor for reduced drug effectiveness.	Vitamin B_6 supplements may lower plasma levels and efficacy of drug and decrease seizure control.
	Slippery elm	Decreased drug absorption.	Separate doses by at least 2 hours.	Theoretical interaction — clinical significance unknown.
Phenytoin and valproate	Vitamin D	Reduced nutrient effects.	Beneficial interaction possible.	Anticonvulsants induce catabolism of vitamin D through liver induction — prolonged use is associated with increased risk of developing rickets and osteomalacia; therefore, increased intake may be useful with long-term therapy.

Continued

Drug	Herb or supplement	Potential outcome	Recommendation	Evidence/Comments
Valproate	Beta-carotene	Reduced nutrient status.	Observe.	Epileptics who gain weight on valproate were found to have reduced plasma concentrations of beta-carotene and other fat-soluble vitamins — which is reversible after valproate withdrawal. Increased intake may be necessary with long-term therapy.
Antidepressants				
Antidepressants including SSRIs, SNRIs, tricyclics and MAOIs	Albizia	Additive effects.	Observe.	Increased risk of serotonergic syndrome is theoretically possible, as the herb increases serotonin levels, according to in vivo studies — clinical significance unknown.
	Ginkgo biloba	Reduced side effects.	Beneficial interaction possible.	Initial open study produced significant improvement in SSRI-induced sexual dysfunction; however, more recent investigations have been inconclusive. Clinical significance difficult to ascertain.
	Lavender	Additive effects.	Observe — beneficial interaction possible.	Lavender may have additive effects.
	St John's wort	Additive effects.	Avoid unless under medical supervision to monitor dose requirements.	Risk of serotonergic syndrome if combined use is not carefully monitored; however, increased antidepressant activity is also possible with appropriate doses.
	SAMe	Additive effects.	Exercise caution.	Theoretically may increase risk of serotonergic syndrome, and a case report exists; however, an experimental study found that brain SAMe levels were significantly reduced after chronic treatment with imipramine, so may be useful adjunctive therapy.
	Tyrosine	Additive effects.	Avoid unless under medical supervision.	Tyrosine is a precursor for several neurotransmitters, which theoretically increases risk of serotonin syndrome.
	Zinc	Improved drug efficacy.	Beneficial interaction possible.	Clinical study has shown 25 mg/d zinc for 2 weeks improves the efficacy of SSRIs and tricyclic antidepressants.
MAOIs	Tyrosine	Increased side effects.	Avoid — unless under medical supervision.	Some tyrosine may be metabolised to tyramine. Concurrent use with MAOIs may lead to hypertensive crisis.
	Rhodiola	Additive effect.	Observe.	Recent in vitro data suggests inhibition of MAO A by rhodiola extracts. A theoretical interaction exists with MAOI antidepressants. Clinical significance as yet unknown.
Tricyclic antide-pressants	Andrographis	Reduced side effects.	Beneficial interaction possible.	Andrographis may exert hepatoprotective activity against liver damage induced by tricyclic antidepressants.
	Coenzyme Q10	Reduced CoQ10 serum levels.	Beneficial interaction possible.	Increased CoQ10 intake may be required with long-term therapy.

Drug	Herb or supplement	Potential outcome	Recommendation	Evidence/Comments
	St John's wort (reduction in drug plasma levels)	Additive effects.	Avoid unless under medical supervision.	Although St John's wort decreases drug plasma levels of tricyclic antidepressants, it may increase available serotonin.
	St Mary's thistle	Reduced side effects.	Beneficial interaction possible.	St Mary's thistle may exert hepatoprotective activity against liver damage induced by tricyclic antidepressants.
	Vitamin B_2 (riboflavin)	Reduced nutrient absorption.	Monitor for signs and symptoms of B_2 deficiency — beneficial interaction possible.	Tricyclic antidepressants may reduce the absorption of riboflavin. Increased vitamin B_2 intake may be required with long-term therapy.
Amitriptyline	Vitamin B_2 (riboflavin)	Increased nutrient excretion.	Monitor for signs and symptoms of deficiency.	Amitriptyline has been found to increase the renal excretion of riboflavin. Increased dietary intake may be required with long-term therapy.
Imipramine	Vitamin B_3 (niacin)	Additive effects.	Beneficial interaction possible.	A combination of imipramine with L-tryptophan 6 g/day and niacinamide 1500 mg/day has been shown to be more effective for people with bipolar disorder than imipramine alone.
Lithium	Psyllium	Reduced drug absorption.	Separate dose by 1 hour before or after drug.	Soluble fibre may decrease bioavailability of drug.
	Slippery elm	Decreased drug absorption.	Separate doses by at least 2 hours.	Theoretical interaction — clinical significance unknown.
	Vitamin B_{12} (cobalamin)	Reduced nutrient status.	Monitor B_{12} status.	Lithium administration is shown to decrease serum B_{12} concentrations — clinical significance unclear.
Antipsychotic agents				
Haloperidol (e.g. Serenace)	Ginkgo biloba	Increased drug effects and reduced side effects.	Observe — beneficial interaction possible under professional supervision.	Three clinical trials demonstrate that ginkgo increases drug effectiveness.
	Iron	Reduced iron effect.	Monitor iron status.	May cause decreased blood levels of iron — clinical significance unclear. Increased iron intake may be required with long-term therapy.
	Quercetin	Reduced drug side effects.	Beneficial interaction possible. under professional supervision.	According to in vivo studies, co-administration with quercetin dose-dependently reduced haloperidol-induced chewing movements and tongue protrusions.
	Withania	Reduced drug side effects.	Beneficial interaction possible under professional supervision.	According to in vivo studies, withania is beneficial in the treatment of drug-induced dyskinesia — reduced chewing movements and tongue protrusions possible with concurrent use.

Continued

Drug	Herb or supplement	Potential outcome	Recommendation	Evidence/Comments
Phenothiazines (e.g. chlorpromazine, trifluoperazine)	Evening primrose oil	Reduced drug effects.	Avoid concomitant use.	Several case reports suggest that evening primrose oil may reduce seizure threshold and reduce drug effectiveness in patients with schizophrenia treated with phenothiazines.
	Coenzyme Q10	Reduced drug-induced side effects.	Beneficial interaction.	Coenzyme Q10 reduces adverse effects of this drug class on CoQ10-related enzymes NADH-oxidase and succinoxidase.
Chlorpromazine (e.g. Largactil)	Vitamin E	Reduced drug effects.	Observe.	According to in vitro research, vitamin E inhibits drug uptake in human cultured fibroblasts — clinical significance unknown.
Atypical anti-psychotic agents				
Olanzapine (e.g. Clozapine)	Ginkgo	Enhanced drug effects.	Beneficial interaction possible under professional supervision.	According to placebo-controlled trial, ginkgo may enhance drug effect on negative affect refractory schizophrenic patients.
CNS agents				
Cholinergic drugs (tacrine [e.g. Cognex])	Brahmi	Additive effects.	Observe — beneficial interaction possible under professional supervision.	Cholinergic activity has been identified for brahmi, so increased drug activity is theoretically possible.
	Ginkgo biloba	Additive effects.	Observe — beneficial interaction possible.	Cholinergic activity has been identified for ginkgo, so increased drug activity is theoretically possible.
	Lemon balm	Additive effects.	Observe — beneficial interaction possible.	Cholinergic activity has been identified for lemon balm, so increased drug activity is theoretically possible.
	St Mary's thistle	Reduced side effects.	Beneficial interaction possible.	St Mary's thistle may exert hepatoprotective activity against liver damage induced by tacrine.
CNS stimulants	Green tea	Additive effect.	Observe.	Theoretical increase of CNS-stimulant effects of drugs such as nicotine and beta-adrenergic agonists — clinical significance is unknown.
	Guarana	Additive effects.	Exercise caution.	Herb has demonstrated CNS-stimulant activity.
	Tyrosine	Additive effects.	Exercise caution.	Tyrosine is a precursor for several neurotransmitters.
Amphetamines	Tyrosine	Increased side effects.	Observe.	Tyrosine (200 and 400 mg/kg) has been shown to increase side effects of anorexia caused by ephedrine and amphetamine in a dose-dependent manner in rats — clinical significance unknown.
Methylphenidate	Zinc	Improved drug efficacy.	Beneficial interaction possible.	Clinical study of ADHD children with co-administration of 15 mg zinc for 6 weeks demonstrated improved drug efficacy.

Drug	Herb or supplement	Potential outcome	Recommendation	Evidence/Comments
Movement disorders				
L-Dopa (levodopa)	Calcium	Reduced drug absorption.	Separate doses by 2 hours.	L-dopa can form an insoluble complex with calcium.
	Iron	Reduced drug effect.	Separate doses by 2 hours.	May reduce bioavailability of carbidopa and L-dopa, which can form an insoluble complex with iron.
	Kava kava	Reduced drug effects.	Avoid unless under medical supervision.	Theoretical interaction, as dopamine antagonist effects have been reported for kava kava.
	Magnesium	Reduced drug absorption.	Separate doses by 2 hours.	L-dopa can form an insoluble complex with magnesium.
	SAMe	Reduced drug effectiveness.	Observe.	Theoretical interaction, as SAMe methylates levodopa. Interaction not observed clinically.
	Tyrosine	Decreased drug and tyrosine effect.	Avoid unless under medical supervision.	L-Dopa competes with tyrosine for uptake, so concurrent use may decrease uptake of both substances, thereby reducing efficacy.
	Vitamin B_6 (pyridoxine)	Increased nutrient requirements.	Observe — beneficial interaction possible under medical supervision.	L-dopa can cause hyperhomocysteinaemia in Parkinson's disease (PD) patients, relative to vitamin B status. Vitamin B requirements are higher in L-dopa treated patients, as such supplementation may be warranted in PD patients.
	Vitamin C	Reduced side effects.	Beneficial interaction possible.	A case report of co-administration with vitamin C suggests this may reduce drug side effects.
	Zinc	Reduced drug absorption.	Separate doses by 2 hours.	L-Dopa can form an insoluble complex with zinc.
L-Dopa with carbidopa	Iron	Reduced drug effect.	Separate doses by at least 2 hours.	May reduce bioavailability of carbidopa and L-dopa, which can form an insoluble complex with iron.
Sedatives, hypnotics				
CNS sedatives	Eucalyptus	Additive effects.	Exercise caution.	Theoretical interaction, as oral ingestion of eucalyptus has been associated with CNS depression.
	Green tea	Additive effects.	Observe.	Theoretically, high intakes can decrease the CNS-depressant effects of drugs such as benzodiazepines — clinical significance is unknown.
	Guarana	Reduced drug effects.	Observe.	Theoretically, guarana may reduce the sedative effects of drug via its CNS-stimulant effects; however, an in vivo study found no interaction with pentobarbital.

Continued

Drug	Herb or supplement	Potential outcome	Recommendation	Evidence/Comments
	Hops	Additive effects.	Observe.	Additive effects theoretically possible, generating increased sedation; interaction may be beneficial in benzodiazepine withdrawal.
	Kava kava	Additive effects.	Exercise caution. Monitor drug dosage — beneficial interaction possible under medical supervision.	May be useful in benzodiazepine withdrawal.
	Lavender	Additive effects.	Observe — beneficial interaction possible under professional supervision.	Theoretically, lavender may potentiate the effects of sedatives.
	Passionflower	Additive effects.	Exercise caution. Beneficial interaction possible under medical supervision — monitor drug dosage.	Increased sedation; interaction may be beneficial in benzodiazepine withdrawal.
	Valerian	Additive effects.	Observe — beneficial interaction possible under medical supervision.	Increased sedation; interaction may be beneficial in benzodiazepine withdrawal.
Midazolam (e.g. Hypnovel)	St John's wort	Reduced drug effects.	Exercise caution. Monitor for signs of reduced drug effectiveness and adjust the dose if necessary.	St John's wort may increase drug metabolism and so reduce serum levels of drug.
Barbiturates	Albizia	Additive effects.	Exercise caution — beneficial interaction possible under medical supervision.	Potentiating of phenobarbitone-induced sleeping was observed in vivo — clinical significance unknown.
	Andrographis	Additive effects.	Observe — beneficial interaction possible under medical supervision.	Potentiating effects observed in vivo — clinical significance unknown.
	Folate	Reduced drug effects.	Exercise caution. Monitor for signs of reduced drug effectiveness.	Concomitant folic acid use can reduce seizure control — supervision may be required.
	Kava kava	Additive effects.	Exercise caution. Beneficial interaction possible under medical supervision — monitor drug dosage.	Increased sedation effects.
	Lemon balm	Additive effects.	Observe — beneficial interaction possible under medical supervision.	Increased sedation effects; one animal study found increased sedative effects from co-administration of lemon balm and pentobarbital — clinical significance unknown.

Drug	Herb or supplement	Potential outcome	Recommendation	Evidence/Comments
	Passionflower	Additive effects.	Exercise caution. Beneficial interaction possible under medical supervision — monitor drug dosage.	Additive CNS sedation is theoretically possible.
	St John's wort (may not relate to low-hyperforin-containing products)	Reduced drug effects.	Avoid — monitor drug requirements. When St John's wort is started or ceased, monitor serum levels and alter drug dosage as required.	St John's wort induces CYP enzymes and P-glycoprotein, so can reduce drug serum levels.
	Slippery elm	Decreased drug absorption.	Separate doses by at least 2 hours.	Theoretical interaction — clinical significance unknown.
	Valerian	Additive effects.	Observe — beneficial interaction possible under medical supervision.	Increased sedation; interaction may be beneficial in benzodiazepine withdrawal.
	Vitamin B_6 (pyridoxine)	Reduced plasma levels and drug effects.	Caution. Monitor for drug effectiveness.	Concomitant B_6 use can reduce seizure control — supervision may be required.
	Withania	Additive effects.	Observe — beneficial interaction possible under medical supervision	Theoretically may increase sedation.
Benzodiazepines	Chamomile	Additive effects.	Observe — beneficial interaction possible under medical supervision.	Theoretically, an additive effect can occur with concurrent use.
	Kava kava	Additive effects.	Exercise caution. Beneficial interaction possible under medical supervision — monitor drug dosage.	Combination has been used to ease symptoms of benzodiazepine withdrawal under medical supervision.
	Passionflower	Additive effects at high doses.	Exercise caution. Beneficial interaction possible under medical supervision — monitor drug dosage.	May be useful in benzodiazepine withdrawal.
	St John's wort	Decreased drug effects.	Exercise caution — monitor for signs of reduced drug effectiveness.	St John's wort induces CYP enzymes and P-glycoprotein, so can reduce drug serum levels.

Continued

Drug	Herb or supplement	Potential outcome	Recommendation	Evidence/Comments
	Valerian	Additive effects.	Observe — beneficial interaction possible under medical supervision.	Combination has been used to ease symptoms of benzodiazepine withdrawal under medical supervision.
	Withania	Additive effects.	Observe — beneficial interaction possible under medical supervision.	Increased sedative effect theoretically possible.
CONTRACEPTIVE AGENTS				
Combined oral contraceptive agents				
Oral contraceptive pill (OCP)	Chaste tree	Reduced herb effects.	Observe.	There has been speculation as to whether chaste tree is effective when OCP is being taken. Several clinical studies conducted in women taking OCP have confirmed that chaste tree still reduces symptoms of premenstrual syndrome.
	Folate	Reduced folate levels.	Beneficial interaction possible.	Folate levels are reduced with long-term use. Increased intake may be required with long-term therapy.
	Licorice	Increased side effects.	Observe. Exercise caution with high-dose licorice (> 100 mg/day glycyrrhizin) or long-term use (> 2 weeks). Monitor patients closely.	Increased risk of side effects such as hypokalaemia, fluid retention and elevated blood pressure have been noted in case reports.
	St John's wort	Reduced drug effects.	Exercise caution — avoid use with low-dose OCP.	Breakthrough bleeding has been reported in 12 cases, which may indicate decreased effectiveness. Caution related to hyperforin content. Recent investigations demonstrate low hyperforin extracts appear safe with OCP use.
	Vitamin A	Increased vitamin A levels.	Exercise caution with large doses of retinol.	OCP increases serum vitamin A levels due to longer storage in the liver.
	Vitamin B_2 (riboflavin)	Reduced vitamin B_2 levels.	Beneficial interaction possible.	OCP may increase demand for vitamin B_2. Increased intake may be required with long-term therapy.
	Vitamin B_3 (niacin)	Reduced vitamin B_3 levels.	Beneficial interaction possible.	Increased intake may be required with long-term therapy.
	Vitamin B_5 (pantothenic acid)	Reduced vitamin B_5 levels.	Beneficial interaction possible.	Increase dietary intake of foods rich in vitamin B_5 or consider supplementation.
	Vitamin B_6 (pyridoxine)	Reduced vitamin B_6 levels.	Beneficial interaction possible.	OCP may induce pyridoxine deficiency. Increase dietary intake of foods rich in vitamin B_6 or consider supplementation.

Drug	Herb or supplement	Potential outcome	Recommendation	Evidence/Comments
	Vitamin B_{12} (cobalamin)	Reduced vitamin B_{12} levels.	Observe for signs and symptoms of B_{12} deficiency — beneficial interaction possible.	OCP users showed significantly lower concentrations of cobalamin than controls in a clinical study; however, this may be due to an effect upon B_{12}-binding proteins. Increased intake may be required with long-term therapy.
ENDOCRINE AND METABOLIC DISORDERS				
Adrenal steroid hormones				
Corticosteroids	Calcium	Reduced side effects. Reduced nutrient status.	Beneficial interaction possible.	Through inhibiting vitamin D-mediated calcium absorption, overall levels may be decreased. Increased calcium intake may be required with long-term therapy.
	Chromium	Reduced side effects.	Beneficial interaction possible.	Corticosteroids increase urinary losses of chromium, and chromium supplementation has been shown to aid in recovery from steroid-induced diabetes mellitus.
	Licorice	Additive effects.	Beneficial interaction possible but patients should be monitored closely for corticosteroid excess.	Concurrent use of licorice preparations potentiates the effects of topical and oral corticosteroids (e.g. prednisolone) as glycyrrhizin inhibits the metabolism of prednisolone. Some practitioners use licorice to minimise requirements for, or to aid in withdrawal of, corticosteroid medications.
	Vitamin B_{12} (cobalamin)	Reduced nutrient status.	Monitor nutrient status — beneficial interaction possible.	Decreased B_{12} levels have been identified in serum and cerebrospinal fluid of multiple sclerosis patients following high-dose 1000 mg/10 days IV methylprednisolone. Supplementation may be indicated.
	Vitamin C	Reduced vitamin C effects.	Beneficial interaction possible.	May increase requirement for vitamin C based on in vitro and in vivo data. Increased intake may be required with long-term therapy.
	Vitamin D	Reduced nutrient status.	Beneficial interaction possible.	Decreases levels of active vitamin D via an unknown mechanism. During long-term therapy of oral or inhaled corticosteroids, vitamin D supplementation should be considered.
Betamethasone	L-Carnitine	Additive effects.	Beneficial interaction possible.	RCT has shown that a combination of low-dose betamethasone (2 mg/day) and L-carnitine (4 g/5 days) was more effective in preventing respiratory distress syndrome (7.3% vs 14.5%) and death (1.8% vs 7.3%) in preterm infants than high-dose betamethasone given alone (8 mg/2 days).
Agents affecting calcium and bone metabolism				
Alendronate (e.g. Fosamax) and etidronate (e.g. Didronel)	Calcium	Reduced drug absorption.	Separate doses by at least 2 hours.	Calcium may reduce drug absorption; however, adequate calcium is required for optimal drug effects.
	Iron	Reduced drug absorption.	Separate doses by at least 2 hours.	

Continued

Drug	Herb or supplement	Potential outcome	Recommendation	Evidence/Comments
	Magnesium	Reduced drug absorption.	Separate doses by at least 2 hours.	Magnesium may reduce drug absorption; however, adequate magnesium is required for optimal drug effects.
	Zinc	Reduced drug absorption.	Separate doses by at least 2 hours.	
Gonadal hormones				
Oestrogen	Chromium	Improved nutrient status.	Beneficial effects.	Women receiving HRT appear to have improved chromium status. Combination therapy has been suggested to inhibit IL-6.
	Hops	Additive effects.	Observe.	Theoretical interaction, based on mild oestrogenic effect of hops.
	Red clover	Reduced drug effects.	Observe.	Theoretically, if taken in large quantities phyto-oestrogens may compete with synthetic oestrogens for receptor binding; however, a review considered 2 mg/kg of red-clover-derived isoflavones to be a safe dose for most patients.
Oestrogen and progesterone	Calcium	Additive effects.	Beneficial interaction possible.	Possible beneficial interaction on bone mineralisation.
	Licorice	Increased side effects.	Observe. Exercise caution with high-dose licorice or long-term use (> 2 weeks).	OCP can increase sensitivity to glycyrrhizin side effects such as hypertension, fluid retention, hypokalaemia.
Testosterone	Licorice	Altered testosterone effect.	Observe. Monitor testosterone levels.	Contradictory evidence suggests possible effects on testosterone levels.
	Saw palmetto	Reduced drug effectiveness.	Observe. Monitor drug efficacy.	Theoretically may reduce effectiveness of therapeutic androgens.
Haemopoietic agents				
Erythropoietin	Ginseng — Korean	Enhanced drug effects.	Beneficial interaction possible.	The total saponin fraction has been shown to promote haemopoiesis — clinical significance for total herb unknown.
	Iron	Additive pharmacological effect.	Beneficial interaction possible.	IV iron supplementation demonstrated improved success of darbepoetin in chemotherapy-related anaemia without iron deficiency without increasing toxicity.
	Withania	Enhanced drug effects.	Beneficial interaction possible.	Animal studies indicate herb increases haematopoiesis — clinical significance unknown.

Drug	Herb or supplement	Potential outcome	Recommendation	Evidence/Comments
Antidiabetic agents				
Thioglitazones (e.g. rosiglitazone and pioglitazone)	Quercetin	Enhanced drug effects.	Exercise caution.	Due to potential for toxicity careful monitoring of hepatic and cardiac function is required.
Sulphonylurea antidiabetic (e.g. gliclazide)	St John's wort	Reduced drug effects.	Avoid — unless under professional supervision — monitor drug effectiveness.	St John's wort found to induce significant clearance of gliclazide.
Hypoglycaemic agents				
Hypoglycaemic (e.g. metformin) agents. Adverse effects associated with increased hypoglycaemic effects include sweating, hunger, depression, tremor and headaches.	Aloe vera	Additive effects.	Observe.	Oral aloe vera may have hypoglycaemic activity, so additive effects are theoretically possible.
	Andrographis	Additive effects.	Exercise caution — blood glucose levels should be checked regularly — beneficial interaction possible under professional supervision.	Andrographis has hypoglycaemic activity comparable to that of metformin in vivo, so additive effects are theoretically possible.
	Bilberry	Additive effects.	Observe.	Animal study identified that the constituent myrtillin exerts hypoglycaemic actions — relevance for bilberry unclear.
	Bitter melon	Additive effects.	Exercise caution. Monitor drug requirements — possible beneficial effect under professional supervision.	
	Chromium	Additive effects.	Exercise caution. Monitor drug requirements — beneficial interaction possible under professional supervision.	Clinical studies have shown that chromium has hypoglycaemic activity in some individuals.

Continued

Drug	Herb or supplement	Potential outcome	Recommendation	Evidence/Comments
	Cinnamon	Additive effects.	Observe — potentially beneficial interaction under professional supervision.	Clinical studies have produced contradictory results.
	Damiana	Additive effects.	Observe.	Theoretically possible — clinical significance is unknown.
	Elder	Additive effects.	Observe.	Hypoglycaemic effects demonstrated in vitro — clinical significance is unknown.
	Eucalyptus	Additive effects.	Exercise caution — monitor blood glucose levels.	If used orally in combination with glucose-lowering agents may contribute to hypoglycaemia.
	Fenugreek	Additive effects.	Exercise caution — blood glucose levels should be checked regularly. Beneficial interaction possible under professional supervision.	
	Ginseng — Siberian	Additive effects.	Observe.	Speculation is based on IV use in animal studies and has not been observed in humans with oral dose forms.
	Green tea	Additive effects.	Observe.	High intake of caffeine-containing drinks can increase blood sugar; however, green tea is reported to be hypoglycaemic, which may negate this effect — clinical significance of combination uncertain.
	Gymnema sylvestre	Additive effects.	Exercise caution. Interaction may be beneficial — reduction in drug dose may be achieved.	Gymnema may theoretically enhance blood-glucose-lowering effects of insulin and hypoglycaemic agents.
	Horse chestnut	Additive effects.	Observe — monitor blood glucose levels.	Horse chestnut exerts hypoglycaemic activity. Concurrent use with hypoglycaemic agents requires monitoring of blood glucose levels — clinical significance is unclear.
	Myrrh	Additive effects.	Exercise caution — blood glucose levels should be checked regularly. Beneficial interaction possible.	Myrrh has been shown to increase glucose tolerance in both normal and diabetic rats — clinical significance unknown.
	Oats	Additive effects.	Exercise caution — beneficial interaction possible under medical supervision. Insulin requirements should be monitored.	In an uncontrolled pilot study, an oatmeal intervention reduced insulin requirements by 42.5%.
	Olive leaf extract	Additive effects.	Beneficial interaction possible under professional supervision — drug dose may need modification.	Olive leaf has demonstrated hypoglycaemic activity in animal models. Theoretically an interaction is possible, though speculative.

Drug	Herb or supplement	Potential outcome	Recommendation	Evidence/Comments
	Psyllium	Additive effects.	Beneficial interaction possible under professional supervision. Drug dose may need modification.	Psyllium has clinically demonstrated a capacity to slow the absorption of glucose and modulate glucose response.
	Vitamin B_3 (niacin)	Increased drug requirement.	Exercise caution. Monitor drug effectiveness	Niacin may affect glycaemic control and increase fasting blood glucose levels, so medication doses may need to be reviewed.
Metformin	Vitamin B_{12} (cobalamin)	Decreased vitamin B_{12} levels.	Observe — monitor for signs and symptoms of deficiency.	In patients with type 2 diabetes, metformin has been shown to reduce B_{12} levels and increase homocysteine. Supplementation may be beneficial.
Sulfonylureas (e.g. glibenclamide)	Coenzyme Q10	Reduced drug side effects.	Beneficial interaction.	Co-administration reduces side effects of this drug class on CoQ10-related enzymes NADH-oxidase.
Thyroid hormones and antithyroid agents				
Levothyroxine (e.g. Oroxine)	Aloe vera	Decreased drug levels.	Observe.	Reduced serum levels of T3 & T4 have been reported in one IV study. Single case report of depressed thyroid hormones in patient ingesting 10 mL of aloe juice daily for 11 months. Hormone levels returned to normal after discontinuing aloe.
	Calcium	Reduced drug absorption.	Separate doses by 2–4 hours.	Calcium and thyroxine form an insoluble complex.
	Celery	Decreased drug effect.	Observe	One case report suggests that celery extract may reduce drug effects. Clinical significance unknown.
	Horseradish	Increased drug requirement.	Observe. Monitor thyroid function. Dose may need to be adjusted.	Isothiocyanates may inhibit thyroxine formation and be goitrogenic, although this has not been demonstrated clinically.
	Iron	Reduced drug effect	Observe — monitor thyroid function and L-thyroxine dose may need alteration. Separate doses by 2–4 hours.	Iron supplements may decrease absorption of thyroid medication; however, iron deficiency may impair the body's ability to make thyroid hormones.
	Magnesium	Reduced drug absorption.	Separate doses by 2–4 hours.	Magnesium and thyroxine form an insoluble complex together.
	Psyllium	Reduced drug absorption.	Separate dose by 1–½ hour. Dose may need to be adjusted under medical supervision.	Soluble fibre may decrease drug bioavailability.
	SAMe		Exercise caution. Drug monitoring may be warranted.	

Continued

Drug	Herb or supplement	Potential outcome	Recommendation	Evidence/Comments
	Tyrosine	Additive effects.	Observe.	Additive effects theoretically possible, as tyrosine is a precursor to thyroid hormones.
	Withania	Additive effects.	Observe.	An in vivo study reported that daily administration of *Withania somnifera* root extract enhanced serum T4 concentration. One case report of withania-induced thyrotoxicosis exists — further investigation required to confirm.
	Zinc	Reduced drug absorption.	Separate doses by 2–4 hours.	Zinc and thyroxine form an insoluble complex together.
EYE				
Glaucoma preparations				
Timolol eye drops	Coenzyme Q10	Reduced side effects.	Beneficial interaction possible.	A clinical trial of people with glaucoma found that oral CoQ10 reduced cardiovascular side effects of timolol eye drops without affecting intraocular pressure.
GASTROINTESTINAL SYSTEM				
Digestive supplements				
Pancreatin	Folate	Reduced folate absorption.	Separate doses by 2–3 hours.	Monitor for folate efficacy and folate status.
Anti-emetic drugs				
Metoclopramide	Shatavari	Additive effect possible.	Exercise caution.	In animal studies shatavari root exerts similar effects on gastric emptying to those of metoclopramide; therefore, additive effects are possible.
Hyperacidity, reflux and ulcers				
Aluminium-based antacids	Vitamin C	Increased aluminium absorption.	Separate doses by at least 2 hours.	Vitamin C increases the amount of aluminium absorbed.
Antacids	Folate	Reduced folate absorption.	Separate doses by 2–3 hours.	
	Iron	Reduced iron absorption.	Separate doses by at least 2 hours.	Reduced iron effect.
Anti-ulcer drugs				
Sucralfate (e.g. Carafate, Ulcyte)	Vitamin E	Reduced vitamin absorption.	Separate doses by at least 4 hours. Monitor vitamin status.	Increased vitamin intake may be required with long-term therapy.
	Calcium	Reduced calcium absorption.	Monitor calcium status.	Calcium supplementation may be required.

Drug	Herb or supplement	Potential outcome	Recommendation	Evidence/Comments
Gastric-acid inhibitors (proton-pump inhibitors [e.g. omeprazole], H_2-receptor antagonists [e.g. ranitidine])	Cranberry	Adjunct to treatment.	Beneficial interaction possible.	Concurrent use increased vitamin B_{12} absorption.
	Folate	Reduced folate absorption.	Separate doses by 2–3 hours.	
	Iron	Reduced effect of iron.	Monitor for iron efficacy and iron status.	Drug reduces gastric acidity and therefore iron absorption.
	Licorice	Adjunct treatment.	Beneficial interaction.	May enhance ulcer healing.
	St John's wort	Reduced drug effectiveness.	Monitor for signs of reduced drug effectiveness — adjust dose if necessary.	St John's wort decreases levels via CYP induction.
	Vitamin B_{12} (cobalamin)	Reduced B_{12} absorption.	Beneficial interaction possible. Monitor B_{12} status.	Studies show that omeprazole acutely decreases cyanocobalamin absorption in a dose-dependent manner. Supplementation may be required with long-term therapy.
Helicobacter pylori triple-therapy	Garlic	Additive effects.	Observe — interaction may be beneficial.	Garlic inhibits growth of *H. pylori* in vitro and in vivo, and two studies have shown a synergistic effect with omeprazole.
Laxatives				
	Aloe vera	Additive effects.	Exercise caution.	Anthraquinones have significant laxative activity and may increase adverse effects of griping.
GENITOURINARY SYSTEM				
Bladder function disorders				
5-alpha-reductase inhibitors (e.g. finasteride [e.g. Proscar])	Pygeum	Additive effects.	Beneficial interaction possible — drug requirements may need to be modified.	Exerts only a weak inhibition of 5-alpha-reductase.
	Saw palmetto	Additive effects.	Beneficial interaction possible — drug requirements may need to be modified.	Additive effect theoretically possible. Meta-analyses show that herb is beneficial for BPH and in vitro tests show it may also inhibit 5-alpha-reductase activity — clinical significance is unknown.

Continued

Drug	Herb or supplement	Potential outcome	Recommendation	Evidence/Comments
	Stinging nettle root	Additive effects.	Beneficial interaction possible — drug requirements may need to be modified.	Clinical studies show nettle root improves symptoms of BPH.
IMMUNOLOGY				
Immune modifiers				
Cyclosporin	Baical skullcap	Reduced drug effects.	Avoid.	*S. baicalensis* decreased plasma levels in animal model — clinical significance unknown.
	Peppermint oil	Additive effects.	Avoid concurrent use unless under medical supervision.	Peppermint oil has been shown to increase the oral bioavailability of cyclosporin in animal studies — clinical significance unknown.
	Echinacea	Decreased drug effects.	Exercise caution.	Theoretically, the immunostimulant activity of the herb may reduce drug effects — clinical significance unknown.
	Goldenseal	Increased drug effects.	Exercise caution.	RCT found berberine 0.2 g tds × 3 m increased blood concentrations of cyclosporin A in renal transplant patients by 29.3% to that of cyclosporin A. Clinical significance of oral ingestion of goldenseal is unknown.
	Quercetin	Reduced drug effects.	Avoid.	Significant decrease in drug bioavailability demonstrated in animal studies.
	St John's wort	Reduced drug. effects.	Avoid.	Decreases plasma levels significantly within 3 days of concomitant use. Recent clinical study found effect is not significant when low hyperforin products are used.
	St Mary's thistle	Reduced drug side effects but possible increase of drug effects.	Exercise caution.	Decreases hepatotoxicity; however, herb may reduce drug metabolism, leading to increased effects — clinical significance unknown.
Interferon	Baical skullcap	Increased side effects.	Exercise caution.	There have been reports of acute pneumonitis due to a possible interaction between Sho-saiko-to preparation (containing baical skullcap) and interferon, which appears to be due to an allergic–immunological mechanism rather than direct toxicity.
Interferon-alpha	L-Carnitine	Reduced side effects.	Beneficial interaction possible under professional supervision.	Clinical trials with patients being treated with interferon-alpha for hepatitis C found a reduction in fatigue associated with treatment when L-carnitine 2 g/day was co-administered.
Tacrolimus (e.g. Prograf)	St John's wort	Reduced drug effects.	Avoid unless under medical supervision — monitor for signs of decreased drug effectiveness.	Decreased drug serum levels via CYP induction.

Drug	Herb or supplement	Potential outcome	Recommendation	Evidence/Comments
Vaccines				
Cholera	Zinc	Immunoadjuvant effect.	Beneficial interaction possible.	In a clinical study co-administration with zinc acetate improved seroconversion of vibriocidal antibodies in children in both faecal and serum titres.
Diphtheria, tetanus, pertussis (DTP) vaccine	Shatavari	Immunoadjuvant effect.	Beneficial interaction possible.	Animal model demonstrated improved antibody titres and immunoprotection on challenge.
Influenza virus vaccine	Ginseng — Siberian	Reduced side effects.	Beneficial interaction possible.	May reduce the risk of post-vaccine reactions.
INFECTIONS AND INFESTATIONS				
Antibiotics	Probiotics	Reduced side effects.	Beneficial interaction possible.	Reduces gastrointestinal and genitourinary side effects. A meta-analysis of nine studies found that *Lactobacilli* and *Saccharomyces boulardii* successfully prevent antibiotic-induced diarrhoea. Increase intake with antibiotic therapy.
	Soy	Reduced phyto-oestrogen effect.	Inhibits metabolism of isoflavones to equol through inhibition of intestinal microflora.	
	Vitamin B_1 (thiamin)	Reduced endogenous vitamin production.	Beneficial interaction possible.	Increase dietary intake or consider supplementation with long-term therapy.
	Vitamin B_2 (riboflavin)	Reduced endogenous vitamin production.	Beneficial interaction possible.	Increase dietary intake or consider supplementation with long-term therapy.
	Vitamin B_5 (pantothenic acid)	Reduced endogenous vitamin production.	Beneficial interaction possible.	Increase dietary intake or consider supplementation with long-term therapy.
	Vitamin B_6 (pyridoxine)	Reduced endogenous vitamin production.	Beneficial interaction possible.	Increase dietary intake or consider supplementation with long-term therapy.
Aminoglycosides (e.g. gentamicin)	Magnesium	Decreased magnesium absorption.	Exercise caution. Monitor for signs and symptoms of magnesium deficiency.	Aminoglycosides may deplete magnesium levels and result in neuromuscular weakness. Increased magnesium may be required with long-term therapy.
Glycopeptide antibiotics (e.g. vancomycin)	Ginseng — Korean		Beneficial additive effect possible.	In animal studies, co-administration of Korean ginseng and vancomycin treated for *Staphylococcus aureus* demonstrated 100% survival compared to 67% of animals treated with Korean ginseng or 50% of animals treated with vancomycin. Clinical human studies required.

Continued

Drug	Herb or supplement	Potential outcome	Recommendation	Evidence/Comments
Quinolone antibiotics (e.g. norfloxacin [e.g. Noroxin])	Calcium	Reduced drug absorption.	Separate antibiotic dose by at least 2 hours before or 4 hours after oral calcium.	
	Dandelion	Reduced drug absorption.	Separate doses by at least 2 hours.	Reduced drug absorption observed in an experimental study.
	Iron	Reduced drug absorption.	Take drug 2 hours before or 4–6 hours after iron dosing — monitor patient for antibiotic efficacy.	
	Magnesium	Reduced drug absorption.	Separate antibiotic dose by taking at least 2 hours before or 4 hours after oral magnesium.	
	Quercetin	Reduced drug effect.	Exercise caution.	Theoretical concern based on in vitro studies as quercetin may compete for bacterial binding site with antibiotics.
	Zinc	Reduced drug and zinc absorption.	Separate doses by at least 2 hours.	Complex formation between zinc and quinolones results in reduced absorption of both substances, with potential reduction in efficacy.
Tetracycline antibiotics (e.g. minocycline [e.g. Minomycin], doxycycline)	Calcium	Reduced drug and calcium absorption.	Separate doses by at least 2 hours.	Tetracyclines form insoluble complexes with calcium, thereby reducing its absorption.
	Iron	Reduced drug effect.	Separate doses by at least 4 hours.	Initial studies indicated tetracyclines form insoluble complexes with iron, thereby reducing its absorption. More recent investigations have found no effect on erythrocyte iron uptake. Monitor iron efficacy during long-term tetracycline use.
	Magnesium	Reduced drug and magnesium absorption.	Separate doses by at least 2 hours.	Tetracyclines form insoluble complexes with iron, thereby reducing its absorption.
	Vitamin A	Increased side effects.	Avoid.	Concomitant use may increase side effects such as headaches. Long-term use increases the risk of pseudotumour cerebri.
	Vitamin B_{12} (cobalamin)	Reduced drug absorption.	Separate doses by at least 2 hours.	B complexes containing B_{12} may significantly reduce the bioavailability of tetracycline hydrochloride.
	Zinc	Reduced drug and zinc absorption.	Separate doses by at least 2 hours.	Complex formation between zinc and tetracycline results in reduced absorption of both substances, with potential reduction in efficacy.

Drug	Herb or supplement	Potential outcome	Recommendation	Evidence/Comments
Other antibiotics and anti-infectives (trimethoprim [e.g. Triprim])	Folate	Reduced folate levels; reduced drug toxicity.	Exercise caution — beneficial interaction possible under medical supervision.	Monitor folate status; increased folate intake may be required with long-term or high-dose therapy.
Anthelmintic drugs				
Albendazole	Ginseng — Korean	Reduced drug effects.		In animal studies, co-administration found to accelerate intestinal clearance of anthelmintic; clinical significance unknown.
Antileishmanial drug				
Stibanate	Quercetin	Improved drug effect.	Beneficial interaction possible.	Concurrent use with quercetin appears to improve drug efficacy and reduce condition side effects of anaemia and parasitaemia.
Antimalarials				
Chloroquine (e.g. Chlorquin)	Vitamin E	Reduced drug effects.	Observe.	According to in vitro research, vitamin E inhibits drug uptake in human cultured fibroblasts — clinical significance unknown.
Pyrimethamine (e.g. Daraprim)	Folate	Reduced folate effects.	Beneficial interaction possible with folinic acid.	Impaired folate utilisation occurs with drug use — supplementation may be required.
Antituberculotics and antileprotics				
Cycloserine and isoniazid	Vitamin B_6 (pyridoxine)	Reduced B_6 levels.	Beneficial interaction possible.	Drug may induce pyridoxine deficiency. Increased dietary intake of vitamin B_6 rich foods or supplementation may be required with long-term therapy.
Isoniazid	Vitamin B_3 (niacin)	Reduced B_3 levels.	Beneficial interaction possible.	Prolonged isoniazid therapy (the drug replaces niacinamide in NAD) may induce pellagra. Increased vitamin intake may be required with long-term therapy.
	Vitamin E	Reduced vitamin absorption.	Separate doses by at least 4 hours and monitor vitamin status.	Increased vitamin intake may be required with long-term therapy.
Rifampicin and isoniazid	Vitamin D	Reduced vitamin D levels.	Beneficial interaction possible.	Drugs reported to induce catabolism of vitamin D. May be a concern for subjects already at risk of compromised vitamin status. Increase vitamin D intake with long-term therapy.
Antiviral agents				
Antiretroviral drugs	Vitamin B_3 (niacin)	Reduced drug side effects.	Beneficial interaction under professional supervision.	Extended release niacin may improve the dyslipidaemia associated with antiretroviral therapy and is considered a safe and effective therapeutic option.

Continued

Drug	Herb or supplement	Potential outcome	Recommendation	Evidence/Comments
HIV drugs (e.g. zidovudine [AZT, e.g. Retrovir])	L-Carnitine	Reduced carnitine levels.	Beneficial interaction possible.	In vitro studies indicate prevention of muscle damage due to carnitine depletion. Increased intake may be required with long-term therapy.
	Ginseng — Korean	Delayed viral resistance.	Beneficial interaction possible.	Long intake of Korean ginseng in HIV-1 infected patients demonstrated delay in resistance mutation to zidovudine.
HIV non-nucleoside transcriptase inhibitors	St John's wort	Reduced drug effects.	Avoid.	St John's wort increases drug metabolism, thereby reducing drug serum levels.
HIV protease inhibitors	St John's wort	Reduced drug effects.	Avoid.	St John's wort increases drug metabolism, thereby reducing drug serum levels.
Saquinavir	Garlic	Reduced drug effects.	Avoid until safety can be established.	Clinical studies have generated conflicting results: one clinical study found that garlic reduces serum levels of saquinavir and therefore drug efficacy, whereas a subsequent study found no significant effect on drug pharmacokinetics.
	Quercetin	Possible reduced drug effects.	Exercise caution.	Co-administration does not appear to alter saquinavir; however, owing to substantial subject variability of drug concentrations caution should be exerted until more is known.
MUSCULOSKELETAL SYSTEM				
Non-steroidal anti-inflammatory drugs				
	Celery seed extract	Reduced side effects.	Beneficial interaction possible.	Gastroprotective activity seen in animal model.
	Chamomile	Reduced side effects.	Interaction is beneficial.	Gastroprotective activity seen in animal model.
	Chondroitin	Additive effects.	Beneficial interaction possible. Drug dosage may require modification.	May enhance the anti-inflammatory effects of the NSAID.
	Colostrum	Reduced side effects.	Interaction is beneficial.	Has gastroprotective activity.
	Devil's claw	Additive effects.	Beneficial interaction possible. Drug dosage may require modification.	May enhance the anti-inflammatory effects of the NSAID.
	Fish oils	Additive effects.	Beneficial interaction possible. Drug dosage may require modification.	May enhance the anti-inflammatory effects of the NSAID.

Drug	Herb or supplement	Potential outcome	Recommendation	Evidence/Comments
	Ginger	Additive effects.	Beneficial interaction possible. Drug dosage may require modification.	May enhance the anti-inflammatory effects of NSAIDs at high doses.
	Glucosamine	Additive effects.	Beneficial interaction possible. Drug dosage may require modification.	Theoretically may enhance the anti-inflammatory effects of the NSAID.
	Glutamine	Reduced side effects.	Beneficial interaction possible.	May ameliorate the increased intestinal permeability caused by indomethacin.
	New Zealand green-lipped mussel	Additive effects.	Beneficial interaction possible. Drug dosage may require modification.	Anti-inflammatory activity reported in a clinical study — may enhance the anti-inflammatory effects of the NSAID.
	Stinging nettle	Additive effects.	Beneficial interaction possible. Drug dosage may require modification.	Anti-inflammatory activity reported in a clinical study — may enhance the anti-inflammatory effects of the NSAID.
	SAMe	Additive effects.	Beneficial interaction possible. Drug dosage may require modification.	Anti-inflammatory activity reported in a clinical study — may enhance the anti-inflammatory effects of the NSAID.
	Vitamin E	Additive effects.	Beneficial interaction possible. Drug dosage may require modification.	May enhance the pain-modifying effects of the NSAID when used in high doses for RA.
	Willow bark	Additive effects.	Beneficial interaction possible. Drug dosage may require modification.	May enhance the anti-inflammatory effects of the NSAID.
	Zinc	Reduced absorption.	Separate doses by at least 2 hours.	
Diclofenac sodium (topical)	Licorice	Additive effects.	Beneficial interaction possible.	In vitro studies have shown that the addition of glycyrrhizin enhanced the topical absorption of diclofenac sodium — significance for licorice unknown.
Sulfasalazine (e.g. Salazo-pyrin)	Folate	Reduced drug absorption.	Separate doses by 2–3 hours.	
	Iron	Reduced drug and iron effects.	Separate doses by at least 2 hours.	May bind together and reduce absorption of both.

Continued

Drug	Herb or supplement	Potential outcome	Recommendation	Evidence/Comments
NEOPLASTIC DISORDERS				
Chemotherapy	Ginseng — Korean	Reduced side effects. May improve drug response.	Beneficial interaction possible under medical supervision but further research required to confirm.	Preliminary evidence suggests Korean ginseng may reduce nausea and vomiting associated with chemotherapy and radiation by antagonising serotonin receptors. Ginseng may also sensitise cancer cells to chemotherapeutic agents.
	Ginseng — Siberian	Reduced drug effects — improved treatment tolerance.	Exercise caution — possible beneficial interaction under medical supervision but further research required to confirm.	Increased tolerance for chemotherapy and improved immune function demonstrated in women with breast and ovarian cancer. Theoretically, co-administration may reduce drug effects; however, improves immune function.
	L-Glutamine	Reduced side effects.	Beneficial interaction possible under medical supervision.	Number of clinical trials have demonstrated that glutamine supplementation improves side effects such as oral pain and inflammation, increased gut permeability and reduced lymphocyte count.
	Rosemary	Increased drug effects of P-gp substrates.	Exercise caution with concentrated extracts until clinical significance determined.	Inhibits P-glycoprotein, so may affect the bioavailability of P-gp substrates.
	Vitamin A	May improve drug response.	Beneficial interaction possible under medical supervision but further research required to confirm.	Adjunctive treatment may improve drug response; consider individual patient characteristics, form and presentation of cancer, and drugs before administration.
	Vitamin C	May enhance anti-tumour activity.	Beneficial interaction possible.	Controversial — further research required.
	Withania	Reduced side effects.	Observe. Beneficial interaction possible under medical supervision but further research required to confirm.	Animal studies suggest a potential role for withania as an adjunctive treatment during chemotherapy for the prevention of drug-induced bone marrow suppression — clinical significance unknown.
Myelosuppression	Echinacea	Reduced side effects.	Beneficial interaction possible under professional supervision.	Use of echinacea between chemotherapy treatment cycles theoretically may improve white cell counts and reduce dose limiting toxicities on myelopoeisis.
Anti-oestrogen (e.g. Tamoxifen)	Hops	Reduced drug effects.	Exercise caution until confirmed clinically.	Theoretically hops may alter the effectiveness of these drugs owing to the herb's oestrogenic activity.

Drug	Herb or supplement	Potential outcome	Recommendation	Evidence/Comments
	Soy	May enhance drug effect.	Potential beneficial interaction under professional supervision.	Recent large prospective study found soy isoflavones consumed at comparative levels to those in Asian populations may reduce the risk of cancer recurrence in women receiving tamoxifen therapy and does not appear to interfere with tamoxifen efficacy. In vivo studies indicate soy isoflavone daidzein may enhance tamoxifen activity against breast cancer burden and incidence — usual dietary intake appears safe but the safety of concentrated extracts is yet to be established.
	Vitamin B_3 (niacin)	Improved drug activity and mitochondrial function.	Beneficial interaction possible under professional supervision.	The adjunct of B_2, B_3 and CoQ10 to tamoxifen therapy demonstrated both improved mitochondrial antioxidant status and antitumour activity. Exact mechanism of niacin is unclear; however, combination therapy may be advantageous.
	Vitamin C	Enhanced drug effects.	Beneficial interaction possible under professional supervision.	In vivo study indicated vitamin C enhanced tamoxifen antitumour activity — potentially beneficial but difficult to assess.
Proteasome inhibitor (e.g. Bortezomib, velcade)	Green tea	Reduced drug effects.	Avoid.	In vitro and in vivo green tea extract almost completely blocked the effects of bortezomib.
	Vitamin C	Reduced drug effects.	Avoid.	Vitamin C inactivated drug activity in vitro.
Topoisomerase enzyme inhibitor (e.g. Irinotecan)	St John's wort	Reduced drug effects.	Exercise caution. Monitor for signs of reduced drug effectiveness and adjust the dose if necessary.	St John's wort may increase drug metabolism and so reduce serum levels of drug.
Topoisomerase enzyme inhibitor (e.g. Etoposide)	Vitamin C	Enhanced drug effects.	Beneficial interaction possible under medical supervision.	Vitamin C enhanced the antitumour activity of etoposide in vitro — potentially beneficial but difficult to assess.
Alkylating agents				
Cyclophosphamide	Astragalus		Possibly beneficial under professional supervision.	
	Echinacea	Increased drug effects.	Avoid in autoimmune disease.	Echinacea appears to increase the immunostimulatory effect of low-dose cyclophosphamide — clinical significance unknown.
	Rhodiola	Enhanced drug effects and reduced drug-side effects.	Beneficial interaction under professional clinical supervision.	In animal models combination therapy has demonstrated enhanced antitumour and antimetastatic action. In addition reduced drug-toxicity in bone marrow was observed.
	Turmeric	Reduced drug effects.	Avoid until confirmed clinically.	Animal studies indicate reduced drug efficacy.

Continued

Drug	Herb or supplement	Potential outcome	Recommendation	Evidence/Comments
	Withania	Reduced drug effects. Reduced side effects/ toxicity.	Exercise caution.	The ability to stimulate stem-cell proliferation has led to concerns that withania could reduce cyclophosphamide-induced toxicity and therefore reduce its usefulness in cancer therapy, although preliminary animal studies indicate a potential role as a potent and relatively safe radiosensitiser and chemotherapeutic agent. Theoretically it may also decrease the effectiveness of other immunosuppressant drugs.
	Vitamin C	Enhanced drug effects.	Beneficial interaction possible under professional supervision.	In vivo study demonstrated enhanced drug effects; potentially beneficial but difficult to assess.
	Herbs with immunostimulant properties (e.g. echinacea, andrographis, astragalus, baical skullcap, garlic, Korean ginseng, pelargonium, Siberian ginseng)	Reduced drug effects.	Observe.	Theoretically, immunostimulating agents may reduce drug effectiveness; however, clinical significance is unknown.
Antibiotic cytotoxics				
Doxorubicin (e.g. adriamycin)	Black cohosh	Increased drug cytoxicity.	Avoid until safety can be confirmed.	Black cohosh increased the cytotoxicity of doxorubicin in experimental model; clinical significance unknown.
	L-Carnitine	Reduced side effects.	Beneficial interaction possible. Use only under professional supervision.	Animal and human studies suggest that long-term carnitine administration may reduce the cardiotoxic side effects of adriamycin — further research required.
	Coenzyme Q10	Reduced side effects.	Beneficial interaction possible.	Animal and human studies suggest that the cardiotoxic side effects of adriamycin are reduced with CoQ10 supplementation — further research required.
	Ginkgo biloba	Reduced side effects.	Beneficial interaction possible.	Animal studies suggest ginkgo reduces hyperlipidaemia and proteinuria associated with adriamycin-induced nephropathy, which may enhance drug therapeutic index. Clinical trials have not been conducted to confirm this activity. In vivo research suggests that ginkgo can prevent doxorubicin-induced cardiotoxicity, although no human studies are available to confirm this activity.

Drug	Herb or supplement	Potential outcome	Recommendation	Evidence/Comments
	Quercetin	Reduced side effects.	Beneficial interaction.	In an animal study, administration of quercetin has exerted a protective effect against the cardiotoxic effects of adriamycin; no human studies available. In human breast cancer cells, quercetin appears to inhibit the formation of cardiotoxic doxorubicinol.
	Rhodiola	Reduced drug side effects.	Beneficial interaction under clinical supervision.	Rhodiola is shown to reduce liver dysfunction without altering adriamycin's antitumour effects.
	St Mary's thistle	Increased drug effectiveness and reduced drug side effects.	Beneficial interaction — under professional supervision.	Silymarin reduces cardiotoxicity and possibly chemosensitises resistant cells to anthracyclines.
	Vitamin C	Reduces side effects and enhances therapeutic action.	Beneficial interaction possible.	Vitamin C enhanced the therapeutic drug effect and reduced drug toxicity in vivo. Potentially beneficial but difficult to assess.
	Vitamin E	Reduced side effects.	Beneficial interaction possible.	One study found that oral DL-alpha-tocopheryl acetate (1600 IU/day) prevented doxorubicin-induced alopecia; however, the same dosage failed to prevent alopecia after doxorubicin treatment post-mastectomy for breast cancer and also failed to prevent alopecia in second study.
	Withania	Reduced drug side effects.	Beneficial interaction possible.	In withania-pretreated animals, attenuation of doxorubicin-induced cardiocytoxic side effects occurred.
Bleomycin	Ginkgobiloba	Reduced side effects.	Beneficial interaction possible.	Animal studies suggest ginkgo reduces drug induced oxidative stress and improves drug tolerance. Clinical studies are necessary to confirm this.
Antimetabolites				
Docetaxel	Black cohosh	Increased drug effects.	Exercise caution.	Increased cytotoxicity of docetaxel observed in experimental model — clinical significance unclear.
Methotrexate	Folate	Reduced side effects but may reduce drug response.	Exercise caution in cancer treatment. Observe in other conditions — medical supervision advised.	Methotrexate is a folate antagonist drug; supplementation may reduce toxicity. This action may be problematic in cancer treatment and reduce drug response, but may be beneficial in other uses.
Paclitaxel	Licorice	Additive effects.	Observe. Beneficial interaction may be possible under medical supervision — further research required.	A constituent of licorice has been demonstrated to significantly potentiate the effects of paclitaxel in vitro — clinical significance for licorice unknown.
	Quercetin	Increased drug effects.	Exercise caution. Drug doses may need adjustment — further research required.	Increased drug bioavailability seen in animal study.

Continued

Drug	Herb or supplement	Potential outcome	Recommendation	Evidence/Comments
	Withania	Potentiates chemotherapeutic effect.	Beneficial interaction possible under medical supervision — further research required.	Co-administration in animal studies has demonstrated enhanced chemotherapeutic effects through modulation of protein-bound carbohydrates and marker enzymes. Combination therapy has shown potential in treatment of benzo(a)pyrene-induced lung cancer through increased antioxidant capacity and attenuation of cell proliferation.
Immunosuppressant drugs				
	Andrographis	Reduced drug effects.	Exercise caution.	Immunostimulant activity has been demonstrated in vivo.
	Astragalus	Reduced drug effects.	Exercise caution.	Due to known immunostimulant effects observed clinically.
	Baical skullcap	Reduced drug effects.	Exercise caution.	Due to known immunostimulant effects observed clinically.
	Echinacea	Reduced drug effects.	Exercise caution.	Due to known immunostimulant effects observed clinically.
	Garlic	Reduced drug effects.	Exercise caution.	Due to known immunostimulant effects observed clinically.
	Ginseng — Korean and Ginseng — Siberian	Reduced drug effects.	Exercise caution.	Due to known immunostimulant effects observed clinically.
Cisplatin	Black cohosh	Reduced side effects.	Beneficial interaction may be possible under professional supervision — further research required.	In an experimental breast cancer model, black cohosh decreased the cytotoxicity of cisplatin — clinical significance unknown.
	L-Carnitine	Reduced side effects.	Beneficial interaction possible under professional supervision.	Treatment with carboplatin results in marked urinary losses of L-carnitine. Research into the use of L-carnitine 4 g/day for 7 days showed reduced fatigue from treatment with cisplatin.
	Ginger	Reduced side effects.	Beneficial interaction possible under professional supervision — further research required.	Pretreatment with ginger has restored testicular antioxidant parameters and sperm motility in cisplatin-induced damage — clinical significance unknown.
	Ginkgo biloba	Reduced side effects.	Beneficial interaction possible under professional supervision.	Ginkgo has been indicated in two in vivo studies to reduce nephrotoxic effects of cisplatin. Animal models have indicated the use of ginkgo in protecting against cisplatin-induced cytotoxicity. Clinical trials are required to confirm clinical significance.
	Pelargonium	Reduced drug effectiveness.	Avoid.	Avoid until safety can be established.
	Quercetin	Increased drug effects.	Beneficial interaction theoretically possible under professional supervision.	Pretreatment may sensitise human cervix carcinoma cells to drug according to preliminary research — further research required.

Drug	Herb or supplement	Potential outcome	Recommendation	Evidence/Comments
	St John's wort	Reduced side effects.	Beneficial interaction. Monitor under professional supervision.	Clinical study found St John's wort inhibited cisplatin-induced kidney histological abnormalities. St John's wort did not alter serum drug concentrations.
	St Mary's thistle	Increased drug effects. Reduced side effects.	Beneficial interaction possible under professional supervision.	Preliminary research has shown that this combination may reduce toxicity effects yet enhance antitumour activity — further research required.
	Selenium	Reduced side effects.	Beneficial interaction possible under professional supervision.	In vitro and in vivo studies indicate that selenium may reduce drug-associated nephrotoxicity, myeloid suppression and weight loss — further research required.
	Vitamin C	Increased drug effects — reduced side effects.	Beneficial interaction possible under professional supervision.	In vitro and in vivo studies indicate that vitamin C enhanced the antitumour activity of cisplatin and reduce drug toxicity — potentially beneficial but difficult to assess.
	Vitamin E	Reduced side effects.	Beneficial interaction possible under professional supervision.	A review of 4 clinical trials with concomitant use of vitamin E and cisplatin demonstrated significant reduction in chemotherapy-induced peripheral neuropathy in all trials.
	Withania	Reduced drug effects.	Exercise caution — beneficial interaction may be possible under professional supervision.	The ability to stimulate stem cell proliferation has led to concerns *W. somnifera* could reduce the effectiveness of immunosuppressant drugs.
Interleukin-2-immunotherapy	L-Carnitine	Reduced side effects.	Beneficial interaction possible under professional supervision.	Clinical trials using L-carnitine (1000 mg/day orally) found that it may successfully prevent cardiac complications during IL-2-immunotherapy in cancer patients with clinically relevant cardiac disorders.
Vinca alkaloids				
Vinblastine	Licorice	Has additive effects.	Observe. Beneficial interaction possible under medical supervision.	A constituent of licorice has been demonstrated to significantly potentiate the effects of vinblastine in vitro — clinical significance unknown.
Vincristine	Vitamin C	Has additive effects.	Beneficial interaction possible under medical supervision.	Vitamin C enhanced drug's effect in vivo — potentially beneficial but difficult to assess.
Radiotherapy				
	Zinc	Reduced plasma nutrient status.	Beneficial interaction under professional supervision.	Radiotherapy reduces plasma zinc levels.
NUTRITION				
Anorectics and weight-reducing agents				
Orlistat (e.g. Xenical)	Lutein and zeaxanthin	Reduced vitamin absorption.	Long-term administration may reduce plasma levels.	Increased vitamin intake may be required with long-term therapy.

Continued

Drug	Herb or supplement	Potential outcome	Recommendation	Evidence/Comments
	Lycopene	Reduced vitamin absorption.	Separate doses by at least 2 hours. Monitor vitamin status.	Drugs that reduce fat absorption may reduce lycopene absorption. Increased vitamin intake may be required with long-term therapy.
	Vitamin A	Reduced vitamin absorption.	Separate doses by at least 4 hours. Monitor vitamin status.	Increased dietary intake of food rich in vitamin A or consider supplementation with long-term therapy.
	Vitamin D	Reduced vitamin absorption.	Separate doses by at least 4 hours either side of drug. Monitor vitamin status.	Concurrent supplementation of multivitamin with vitamin D is advised.
	Vitamin E	Reduced vitamin absorption.	Separate doses by at least 4 hours. Monitor vitamin status.	Increased vitamin intake may be required with long-term therapy.
	Vitamin K	Reduced vitamin absorption.	Separate doses by at least 4 hours. Monitor vitamin status.	Increased vitamin intake may be required with long-term therapy.
POISONING, TOXICITY AND DRUG DEPENDENCE				
Agents used in drug dependence				
Methadone	Kava kava	Has additive effects.	Exercise caution.	Increased sedation theoretically possible.
	St John's wort	Reduced drug effects.	Avoid.	Decreases serum levels via CYP induction.
Detoxifying agents, antidotes				
Penicillamine (e.g. D-penamine)	Calcium	Reduced drug effects.	Separate doses by 2 hours.	Combination forms insoluble complex.
	Iron	Reduced drug and iron effects.	Separate doses by at least 2 hours. Do not suddenly withdraw iron.	Sudden withdrawal of iron during penicillamine use has been associated with penicillamine toxicity and kidney damage.
	Magnesium	Reduced drug effects.	Separate doses by 2 hours	Combination forms insoluble complex.
	Vitamin B_6 (pyridoxine)	Reduced B_6 effect.	Beneficial interaction possible.	Drug may induce pyridoxine deficiency — increase intake of vitamin B_6 rich foods or consider supplementation.
	Zinc	Reduced drug effects.	Separate doses by 2 hours.	Combination forms insoluble complex.
RESPIRATORY SYSTEM				
Broncospasm relaxants				
Ephedrine	Tyrosine	Increased side effects.	Observe.	Tyrosine (200 and 400 mg/kg) has been shown to increase side effects of anorexia caused by ephedrine and amphetamine in a dose-dependent manner in rats — clinical significance unknown.

Drug	Herb or supplement	Potential outcome	Recommendation	Evidence/Comments
Theophylline	St John's wort	Reduced drug effects.	Monitor for signs of reduced drug effectiveness and adjust the dose if necessary.	Decreased drug serum levels.
	Vitamin B_6 (pyridoxine)	Reduced B_6 levels	Beneficial interaction possible.	Drug may induce pyridoxine deficiency. Increased intake may be required with long-term therapy.
Expectorants, antitussives, mucolytics and decongestants				
	Adhatoda	Increased drug effects.	Observe.	Results from animal studies show that *Adhatoda vasica* extract exerts considerable antitussive activity when administered orally and is comparable to codeine when cough is due to irritant stimuli.
Phenylpropanolamine (found in Neo-Diophen)	Tyrosine	Increased side effects.	Observe.	Tyrosine (200 and 400 mg/kg) has been shown to increase side effects of anorexia caused by phenylpropanolamine in a dose-dependent manner in rats — clinical significance unknown.
SKIN				
Acne, keratolytics and cleansers				
Isotretinoin (e.g. Roaccutane)	Vitamin A	Has additive effects.	Avoid.	Isotretinoin is a vitamin A derivative, so adverse effects and toxicity may be increased.
Psoriasis, seborrhoea and ichthyosis				
Ketoconazole (e.g. Nizoral)	Vitamin D	Reduced vitamin D effects.	Compromised vitamin status.	Ketoconazole reduces the conversion of vitamin D to its active forms. Increased intake may be required with long-term therapy.
Topical corticosteroids				
Topical corticosteroids (e.g. hydrocortisone)	Aloe vera (topical)	Has additive effects.	Beneficial interaction possible.	In addition to its own anti-inflammatory effects, animal studies have shown that aloe vera increases the absorption of hydrocortisone by hydrating the stratum corneum, inhibits hydrocortisone's antiwound-healing activity and increases wound tensile strength.
OTHER				
Alcohol	Andrographis	Reduced side effects.	Beneficial interaction possible.	May reduce hepatic injury.
	Ginseng — Korean	Reduced side effects.	Beneficial interaction possible.	May reduce hepatic injury.
	Kava kava	Has additive effects.	Observe.	Potentiation of CNS sedative effects have been reported in an animal study; however, one double-blind placebo-controlled study found no additive effects on CNS depression or safety-related performance.
	Magnesium	Reduced vitamin status.	Monitor for deficiency.	Chronic alcohol ingestion may lead to nutrient deficiency — consider increased intake.

Continued

Drug	Herb or supplement	Potential outcome	Recommendation	Evidence/Comments
	St Mary's thistle	Reduced side effects.	Beneficial interaction possible.	May reduce hepatic injury.
	SAMe	Reduced side effects.	Beneficial interaction possible.	May reduce hepatic injury caused by such agents as paracetamol, alcohol and oestrogens.
	Schisandra	Reduced side effects.	Beneficial interaction possible.	May reduce hepatic injury.
	Vitamin B_1	Reduced vitamin status.	Monitor for deficiency.	Chronic alcohol ingestion may lead to nutrient deficiency — consider increased intake.
	Vitamin B_2	Reduced vitamin status.	Monitor for deficiency.	Chronic alcohol ingestion may lead to nutrient deficiency — consider increased intake.
Colchicine	Vitamin A	Reduced vitamin A effects.	Monitor for deficiency — beneficial interaction possible.	Colchicine may interfere with vitamin A absorption and homeostasis.
Dopamine antagonists	Chaste tree	Reduced drug effects.	Observe.	Anatagonistic action theoretically possible.
Hepatotoxic drugs	Andrographis	Reduced side effects.	Beneficial interaction possible.	May exert hepatoprotective activity against liver damage induced by drugs such as paracetamol and tricyclic antidepressants.
	Garlic	Reduced side effects.	Beneficial interaction possible.	May exert hepatoprotective activity against liver damage induced by drugs such as paracetamol.
	Quercetin	Reduced side effects.	Interaction is beneficial.	Exerts hepatoprotective activity.
	St Mary's thistle	Reduced side effects.	Beneficial interaction possible.	May exert hepatoprotective activity against liver damage induced by drugs such as paracetamol.
	SAMe	Reduced side effects.	Beneficial interaction possible.	May exert hepatoprotective activity against liver damage induced by drugs such as paracetamol.
	Schisandra	Reduced side effects.	Beneficial interaction possible.	May exert hepatoprotective activity against liver damage induced by drugs such as paracetamol.
Lipophilic drugs	Chitosan	Reduced drug absorption.	Separate doses by at least 2 hours.	Binds to dietary fats and reduces their absorption and so can also affect the absorption of lipophilic drugs.
PUVA therapy	Celery	Has additive effects	Exercise caution.	While celery has been found to contain psoralens, celery extract does not seem to be photosensitising even after ingestion in large amounts; however, it may increase the risk of phototoxicity with concurrent PUVA therapy.
	St John's wort (hypericin component)	Has additive effects.	Exercise caution.	Hypericin may increase sensitivity to UV radiation.

APPENDIX 3

POISONS INFORMATION CENTRES

EMERGENCIES

For information and advice on emergency treatment of poisoning, overdoses of medicines, bites and stings:
Australia (all states and territories), call **13 11 26** (24-hour line)
New Zealand, call **0800 764 766** (0800 POISON) (24-hour line)

STATE AND TERRITORY CENTRES

Australian Capital Territory

The Canberra Hospital
Yamba Drive
GARRAN 2605
Tel: (02) 6244 3333

New South Wales

The Children's Hospital at Westmead
Locked Bag 4001
WESTMEAD 2145
Tel: (02) 9382 1367

Northern Territory

Royal Darwin Hospital
Rocklands Drive
TIWI 0810
Tel: (08) 8922 8424

Queensland

Brisbane Royal Children's Hospital
Herston Road
HERSTON 4029
Tel: 131 126

South Australia

Women's and Children's Hospital
72 King William Road
ADELAIDE 5006
Tel: (08) 8161 7222

Tasmania

Royal Hobart Hospital
48 Liverpool Street,
HOBART 7001
Tel: (03) 6222 8737

Victoria

Royal Children's Hospital
Flemington Road
PARKVILLE 3052
Tel: (03) 9345 5680

Western Australia

Sir Charles Gairdner Hospital
Hospital Avenue
NEDLANDS 6009
Tel: (08) 9346 2923

OTHER

Australian Sports Drug Agency

Tel: 1800 020 506

APPENDIX 4

RESOURCES: TRAINING, MANUFACTURERS AND INFORMATION

COURSES IN AUSTRALIA

Listed below are universities, schools and colleges in Australia offering undergraduate or postgraduate courses in nutritional medicine, herbal medicine, naturopathy or complementary medicine.

Australian Capital Territory

Australian Institute of Applied Sciences, College of Natural Medicine
1/6 Napier Close, Deakin 2600

Canberra Institute of Technology
GPO Box 826, Canberra 2601

New South Wales

Australasian College of Natural Therapies
PO Box K1356, Haymarket 1240

Charles Sturt University, School of Biomedical Sciences
PO Box 588, Wagga Wagga 2678

College of Nepean Natural Therapeutics
Suite 12/20 Castlereagh St, Penrith 2750

Endeavour College of Natural Health
139 Alexander Street, Crows Nest, Sydney 2065

Gracegrove College
Level 1/723 Hunter St, Newcastle 2300
(PO Box 108, Newcastle 2300)

International Academy of Nutrition
Suite 4/21, Sydney Rd, Manly 2095
(PO Box 370, Manly 2095)

Nature Care College
46 Nicholson St, St Leonards 2065

NSW School of Natural Medicine
202 North Boambee Rd, Coffs Harbour 2450

Southern Cross Herbal School
PO Box 1195, Gosford 2250

Southern Cross University, School of Health & Human Sciences, Natural and Complementary Medicine
PO Box 157, Lismore 2480

Sydney College of Homeopathic Medicine (a campus of Endeavour College of Natural Health)
Level 2, 139 Alexander Street, Crows Nest 2065

University of Newcastle, School of Applied Sciences
University Drive, Callaghan 2308

University of Sydney, Faculty of Pharmacy
Sydney 2006

University of Technology Sydney, College of Traditional Chinese Medicine, Faculty of Science (incorporates the College of TCM)
15 Broadway, Ultimo 2007

University of Western Sydney
Narellan Road, Campbelltown 2560

Queensland

Aromatherapy College of Australia
Suite 3, 16–36 Nile St, Woolloongabba 4102

Australasian College of Natural Therapies
Unit 2, 10 Costin Street, Fortitude Valley 4006

Australian College of Phytotherapy
PO Box 661, Warwick 4370

Australian Institute of Applied Sciences, College of Natural Medicine
11 Beata Street, Stones Corner 4120

Endeavour College of Natural Health (formerly known as Australian College of Natural Medicine)
Brisbane Campus: 362 Water St, Fortitude Valley 4006
Gold Coast Campus: 105 Scarborough St, Southport 4215

Gold Coast Institute of TAFE Academy of Natural Therapies
91 Scarborough St, Southport 4215

Health Schools Australia
PO Box 94, Runaway Bay 4216

Naturopathic Correspondence College of Australia
1066 Dayboro Rd, Kurwongbah 4503

University of Queensland, School of Medicine
PO Box 789, Sanctuary Cove 4212

South Australia

Adelaide Training College of Complementary Medicine
Division 3/297 Montacute Rd, Newton 5074

Endeavour College of Natural Health
88 Currie Street, Adelaide 5000

University of South Australia, Division of Health Sciences
City East Campus, North Terrace, Adelaide 5000

Tasmania

Tasmanian Polytechnic (TAFE Tasmania)
75 Campbell Street, Hobart 7000

Victoria

Australasian College of Nutritional and Environmental Medicine (ACNEM)
10/23–25 Melrose Street, Sandringham 3191

Endeavour College of Natural Health (formerly known as Australian College of Natural Medicine)
City Campus: 368 Elizabeth St, Melbourne 3000

Holmesglen Institute of TAFE
585 Waverley Road, Glen Waverley 3150

National College of Traditional Medicine
1st Floor, 25–29 Devonshire Rd, Sunshine 3020

RMIT School of Health Sciences
Bundoora West Campus, Plenty Rd, Bundoora 3083

Southern School of Natural Therapies
39 Victoria St, Fitzroy 3065

Victoria University, Biomedical and Health Science Department
Ballarat Rd, Footscray 3011

Western Australia

Australian Institute of Holistic Medicine
862 North Lake Rd, Jandakot 6164

Endeavour College of Natural Health (formerly known as Australian College of Natural Medicine)
170 Wellington Street, East Perth 6004

Paramount College of Natural Medicine
11/15 Bonner Drive, Malaga 6090

COURSES IN NEW ZEALAND

Listed below are universities, schools and colleges in New Zealand offering undergraduate or postgraduate courses in nutritional medicine, herbal medicine, naturopathy or complementary medicine.

Bay of Plenty College of Homeopathy
2 Edgecombe Road, Tauranga, NZ 3110

Canterbury College of Natural Medicine
PO Box 4529, Christchurch, NZ 8140

Lotus Holistic Centre
1024 St Aubyn St West, Hastings, Hawkes Bay, NZ 4120

Naturopathic College of New Zealand Ltd
4–6 Lynton St, New Plymouth, NZ 4310

New Zealand School of Acupuncture and Traditional Chinese Medicine
Level 10, Willbank House, 57 Willis Street, Wellington, NZ 6011

South Pacific College of Natural Therapies
8 Arthur Street, Ellerslie, Auckland, NZ 1542

The International College of Herbal Medicine
18B Sirrah St, Okitu, Gisborne, NZ 4010

University of Canterbury (ENZAM New Zealand Centre for Evidenced Based Research into Complementary and Alternative Medicine)
Private Bag 4800, Christchurch, NZ 8140

Waikato Centre for Herbal Medicine Limited
PO Box 15064, Dinsdale, Hamilton, NZ 3243

Wellpark College of Natural Therapies
PO Box 78229, Grey Lynn, Auckland, NZ 1245

COMPLEMENTARY MEDICINE ASSOCIATIONS

Listed below are complementary medicine associations of Australian and New Zealand practitioners and industry.

Australia

Australasian Integrative Medicine Association (AIMA)
Royal Australian College of General Practitioners Building, 1 Palmerston Crescent, South Melbourne, VIC 3205
Chiefly represents medical doctors; however, other healthcare professionals may become associate members.

Australian Complementary Health Association
Ross House, 4th Floor, 247 Flinders Lane, Melbourne, VIC 3000
Represents consumers and practitioners.

Australian Natural Therapies Association (ANTA)
PO Box 657, Maroochydore, QLD 4558
Major association representing complementary medicine practitioners.

Australian Naturopathic Practitioners Association (ANPA)
Suite 36/123 Camberwell Road, East Hawthorn, VIC 3123
Longest-standing naturopathy association in Australia.

Australian Self Medication Industry (ASMI)
Level 22, 141 Walker Street, North Sydney, NSW 2060
Represents companies involved in the manufacture and distribution of over-the-counter consumer healthcare products; peak industry body for the Australia self-care industry.

Australian Traditional Medicine Society (ATMS)
12/27 Bank St, Meadowbank, NSW 2114
Currently Australia's largest professional association of complementary medicine practitioners

Complementary Healthcare Council (CHC)
Unit 2, 1 Napier Close, Deakin, ACT 2600
Peak body representing the complementary healthcare industry (suppliers, retailers, healthcare professionals and consumers).

Complementary Medicine Association (CMA)
Suite 1A, 126 Scarborough Street, Southport, QLD 4215

Federation of Natural and Traditional Therapists (FNTT)
PO Box 168, North Adelaide, SA 5006
Represents several professional associations.

International Aromatherapy and Aromatic Medicine Association
Level 1, 89/91 Burwood Road, Burwood, NSW 2136

National Herbalists Association of Australia (NHAA)
PO Box 45, Concord West, NSW 2138
Longest established association of Western herbal medicine practitioners

New Zealand

New Zealand Association of Medical Herbalists
PO Box 12852, Chartwell, Hamilton, NZ 3248

New Zealand Charter of Health Practitioners
344a Rosedale Road, Albany, North Shore, Auckland, NZ 0632
Represents 80% of total Natural Healthcare practitioner population of New Zealand.

New Zealand Natural Medicine Association
Private Box 303, 236 North Harbour, Auckland, NZ 0751

New Zealand Society of Naturopaths
PO Box 90–170, Victoria Street West, Auckland, NZ 1142

South Pacific Association of Natural Therapists
28 Willow Avenue, Birkenhead, Auckland, NZ 1310

MAJOR MANUFACTURERS OF HERBAL MEDICINES AND NATURAL SUPPLEMENTS

Australia

BioCeuticals
PO Box 6454, Alexandria, NSW 2015

Bio Concepts Pty Ltd
Unit 9/783 Kingsford Smith Drive, Eagle Farm, QLD 4009

DFC Thompson Australia Pty Ltd
23–25 Sefton Rd, Thornleigh, NSW 2120

Dr Vera's Pure Innovation
1800 625934

Eagle Pharmaceuticals
PO Box 927, Castle Hill, NSW 1765

Essential Nutrients Pty Ltd
107A Ledger Road, Beverley, SA 5009

FAB Health
PO Box 7962, Baulkham Hills BC, NSW 2153

Felton, Grimwald & Bosisto's Pty Ltd
61–81 Clarinda Road, Oakleigh South, VIC 3167

Interclinical Laboratories
Unit 6, 10 Bradford Street, Alexandria, NSW 2015

Lipa Pharmaceuticals Pty Ltd
21 Reaghs Farm Rd, Minto, NSW 2566

MediHerb Pty Ltd
PO Box 713, Warwick, QLD 4370

NPD
PO Box 1051, Eagle Farm, QLD 4009

Nutrition Care Pharmaceuticals Pty Ltd
PO Box 153, Dingley, VIC 3172

Olive Leaf Australia
767 Bischoffs Road, Coominya, QLD 4311

Tabco Pty Ltd
26 Roseberry St, Balgowlah, NSW 2093

The Herbal Extract Company of Australia
Unit 9/25 Childs Road, Chippington Norton, NSW 2170

VitaSearch
PO Box 7052, Alexandria, NSW 2015

New Zealand

Alpha Laboratories (NZ) Ltd
16–18 Bowden Road, Mt Wellington, Auckland, NZ 1060
Healtheries of Australia Pty Ltd
PO Box 22045, Otahuhu, Auckland, NZ 1640

RESOURCES USED TO COMPILE THIS BOOK

A book of this type requires careful research and access to quality resources in order to provide balanced and accurate information. Below is a list of many of the reference texts and electronic databases on which the information is based.

Reference texts

Atkinson AJ (ed). Principles of clinical pharmacology. California: Academic Press, 2001.
Battaglia S. The complete guide to aromatherapy. Brisbane: The Perfect Potion, 1995.
Beers MH, Berkow R (eds). The Merck manual of diagnosis and therapy, 17th edn. Whitehouse, NJ: Merck and Co Inc, 2003.
Blumenthal M et al (ed). Herbal medicine: expanded Commission E monographs, Austin, TX: Integrative Medicine Communications, 2000.
Blumenthal M et al. The ABC clinical guide to herbs. Texas: American Botanical Council, 2003.
Bratman S, Kroll D. Natural health bible. Rocklin, CA: Prima Health, 2000.
Braunwald E et al. Harrison's principles of internal medicine. New York: McGraw Hill, 2003.
Brinker F. Herb contraindications and drug interactions, 2nd edn, Portland: Eclectic Medical Publications, 1999.
Bryant B et al. Pharmacology for health professionals. Sydney: Elsevier, 2003.
Como D (ed). Mosby's medical, nursing and allied health dictionary, 6th edn. Philadelphia: Mosby, 2003.
Ernst E et al. The desktop guide to complementary and alternative medicine: An evidence-based approach. St Louis: Mosby, 2001.
Fetrow CW, Avila JR. Professionals handbook of complementary and alternative medicines. Springhouse: Springhouse Corp, 1999.
Fisher C, Painter G. Materia Medica for the Southern Hemisphere. Auckland: Fisher-Painter Publishers, 1996.
Grieve MA. Modern herbal. London: Penguin Books, 1980.
Hendler SS, Rorvik D (eds). PDR for nutritional supplements. Montvale, NJ: Medical Economics Co, 2001.
Hoffmann D. The new holistic herbal. Dorset, UK: Element Books, 1990.
Kumar P, Clark M. Clinical medicine, 5th edn, London: WB Saunders, 2002.
Lininger SW (ed). A–Z guide to drug–herb–vitamin interactions. California: Prima Health, 1999.
Mills S, Bone K. Principles and practice of phytotherapy. London: Churchill Livingstone, 2000.
Mills S, Bone K. The essential guide to herbal safety. Sydney: Elsevier, 2005.
Mills S. The essential book of herbal medicine. London: Penguin Books, 1991.
Murray M. The healing power of herbs. Rocklin, CA: Prima Health, 1995.
Newell CA et al. Herbal medicines: A guide for health care professionals. London: The Pharmaceutical Press, 1996.
Nissen D (ed). Mosby's drug consult. St Louis: Mosby, 2003.
Pelton R et al. Drug-induced nutrient depletion handbook 1999–2000. Hudson, OH: Lexi-Comp, 2000.
Pizzorno J, Murray M. Textbook of natural medicine. St Louis: Elsevier, 2006.
Price S, Price L. Aromatherapy for health professionals, 2nd edn. London: Churchill Livingstone, 2002.
Rang HP et al. Pharmacology, 4th edn. Edinburgh: Churchill Livingstone, 2001.
Shils M (ed). Modern nutrition in health and disease, 9th edn. Baltimore: Williams and Wilkins, 2000.
Skidmore-Roth L. Mosby's handbook of herbs and natural supplements. St Louis: Mosby, 2001.
Thomsen M. Phytotherapy desk reference, 2nd edn. Institute for Phytotherapy, 2001.
Ulbricht CE et al. Natural standard herb and supplement reference. St Louis: Mosby, 2005.
Wahlqvist ML (ed). Food and nutrition, 2nd edn, Sydney: Allen & Unwin, 2002.
Waller DG et al. Medical pharmacology and therapeutics. London: WB Saunders, 2001.
Williamson EM. Dabur Research Foundation and Dabur Ayurvet Ltd. Edinburgh: Churchill Livingstone, 2002.

Public access electronic databases

Some of these may require an access fee.
Entrez-PubMed (National Library of Medicine USA): www.ncbi.nlm.nih.gov/PubMed/
Arbor Nutrition Guide: www.arborcom.com
Integrative Medicine Gateway (IMG; Unity Health Pty Ltd, Australia): www.imgateway.net/wheel.htm
Herbmed: www.herbmed.org
Medscape from WebMD: www.medscape.com
Merck Manual, 17th edn, 1999–2003 (Merck & Co): www.merck.com
Dr Duke's phytochemical and ethnobotanical databases. US Department of Agriculture–Agricultural Research Service–National Germplasm Resources Laboratory. Beltsville Agricultural Research Center, Beltsville, MD. www.ars-grin.gov/duke

Specialist databases

EMBASE.com
FullText Clinicans' Health Channel
Health and Medical Complete
Journals @ OVID (OVID technologies)
Medical Library and Health Module
Micromedex (Thomson Healthcare Series)
Natural Medicines Comprehensive Database (Therapeutic Research Facility): www.naturaldatabase.com
ProQuest
Science Direct (Elsevier Publishing): www.sciencedirect.com
The Cochrane Library

APPENDIX 5

GUIDE TO THE SAFE USE OF COMPLEMENTARY MEDICINES DURING THE PREOPERATIVE PERIOD

This table is intended to provide clinicians with some guidance when advising patients due for surgery about the safe use of complementary medicines (CMs). It is limited to the CMs reviewed in this book, especially those that are known or suspected to increase bleeding or interact with drugs commonly used in the perioperative period. The recommendations are conservative and not likely to be relevant to many low-risk or minor surgical procedures, but it is imperative that each patient be individually assessed before surgery.

CMs are listed alphabetically by common name. The comments section includes a brief description of the type of evidence available to support the recommendation; more detailed information is given in the individual monographs. Several different recommendations are possible. Sometimes there is a recommendation to suspend use 1–2 weeks before surgery, which should provide ample time for bleeding rates to return to normal or potential interactions to be avoided. This is most likely an overestimation of the actual time required. Please note that coumarin-containing and salicylate-containing herbs have not been included in the table unless they have demonstrated antiplatelet or anticoagulant effects in animal or human studies. Sometimes the recommendations are dose dependent; in other cases CM use appears safe but there is a theoretical concern.

It is acknowledged that, in practice, not all surgical patients will be able to follow these recommendations. In situations where bleeding would be a serious complication and a 1-week minimum deferment is not possible, tests of haemostasis prior to surgery should be considered.

It must be reiterated that the clinical relevance of some interactions and adverse effects is unknown and controlled studies in surgical patients are not available. However, it would seem prudent for healthcare providers to become familiar with these medicines, in order to advise patients appropriately and to anticipate, manage or avoid adverse events during the perioperative period.

Common name	Botanical name (where applicable)	Comments	Recommendation
Andrographis	*Andrographis paniculata*	Andrographolide inhibits platelet-activating-factor-induced platelet aggregation in a dose-dependent manner (confirmed clinically) (Amroyan et al 1999, Zhang et al 1994).	Suspend use 1 week before surgery.
Baical skullcap	*Scutellaria baicalensis*	There is a theoretical risk of anticoagulant activity; not observed in clinical trials.	Use under observation but likely to be safe.
Dong quai	*Angelica sinensis*	Dong quai has been found to have potent anticoagulant effects and haemostatic effects. Ferulic acid found in dong quai is reported to inhibit platelet aggregation. A case has been reported of subarachnoid haemorrhage with herbal combination red clover, Siberian ginseng and dong quai.	Suspend the use of high-dose supplements 1 week before surgery.

Common name	Botanical name (where applicable)	Comments	Recommendation
Evening primrose oil (EPO)	Omega-6 essential fatty acids or n-6 fatty acids	Gamma linolenic acid in EPO affects PG synthesis, leading to inhibition of platelet aggregation – clinical significance unknown.	Suspend use of high-dose concentrated products 1 week before surgery; however, safety is difficult to assess.
Feverfew	*Tanacetum parthenium*	Evidence is contradictory as to whether feverfew inhibits platelet aggregation Inhibition of platelet aggregation has been observed in several in vitro studies (Groenewegen & Heptinstall 1990, Marles et al 1992, Voyno-Yasenetskaya et al 1988); however, a small human study found no effects on platelet aggregation (Biggs et al 1982).	Use under observation but likely to be safe.
Fish oils	Omega-3 essential fatty acids or n-3 fatty acids	Multiple clinical studies conducted in surgical patients with no significant increase in bleeding observed (Harris 2007). Some benefits reported (see monograph). Bleeding times increased at very high doses of 12 g/day of n-3 fatty acids (Harris et al 1990).	Usual therapeutic doses are safe according to systematic review of use in surgical patients. Suspend use of high-dose products (12 g/day and higher) 1 week before surgery.
Garlic	*Allium sativum*	Inhibition of platelet aggregation is clinically significant — two cases of postoperative bleeding after excessive dietary intake have been reported (Burnham 1995, German et al 1995). One clinical study found reduced haematocrit values and plasma viscosity (Jung et al 1991).	Usual dietary intakes are likely to be safe. Suspend use of concentrated extracts (> 7 g) 1 week before surgery.
Ginger	*Zingiber officinale*	Standard intake likely to be safe. Oral doses of 4 g/day did not alter platelet aggregation or fibrinogen levels in one clinical study, whereas a high dose of 10 g/day significantly reduced platelet aggregation in another clinical study (Bordia et al 1997).	Usual dietary and therapeutic intakes are likely to be safe. Suspend use of high-dose (10 g/day) concentrated extracts 1 week before surgery.
Ginkgo	*Ginkgo biloba*	At least 10 clinical studies have found no significant effect on bleeding or platelets; however, rare cases of bleeding have been reported. One escalating dose study found that doses of 120 mg, 240 mg or 480 mg given daily for 14 days did not alter platelet function or coagulation (Bal Dit et al 2003).	Use under observation but likely to be safe.
Ginseng — Korean	*Panax ginseng*	Herb inhibits platelet aggregation according to both in vitro and animal studies, but clinical significance unknown. In contrast, the total saponin fraction has been shown to promote haemopoiesis by stimulating proliferation of human granulocyte-macrophage progenitors (Niu et al 2001).	Suspend use 1 week before surgery; however, safety is difficult to assess.
Ginseng — Siberian	*Eleutherococcus senticosus*	Siberian ginseng constituent 3, 4-dihydroxybenzoic acid has demonstrated antiplatelet activity in vivo.	Suspend use 1 week before surgery; however, safety is difficult to assess.
Goji	*Lycium barbarum*	Inhibition of platelet aggregation in vitro — clinical significance unknown. Not demonstrated in human studies.	Use under observation but likely to be safe.

Continued

Common name	Botanical name (where applicable)	Comments	Recommendation
Green tea	*Camellia sinensis*	Shown to exert antiplatelet aggregation and antithrombogenic activities. A case report of excessive daily intake 2.5–4.5 L/day decreased INR.	Usual dietary intake likely to be safe.
Guarana	*Paullinia cupana*	In vitro and in vivo research have identified antiplatelet activity (Bydlowski et al 1991).	Suspend use of concentrated extracts 1 week before surgery.
Kava kava	*Piper methysticum*	Increased sedation due to significant CNS-depressant effects possible. Inhibition of CYP2E1 has been demonstrated in vivo therefore serum levels of CYP2E1 substrates may become elevated (e.g. the anaesthetic drugs). • halothane • isoflurane • methoxyflurane	Use under professional supervision.
Licorice root	*Glycyrrhiza glabra*	Isoliquiritigenin inhibits platelet aggregation (Tawata et al 1992) and glycyrrhizin inhibits prothrombin (Francischetti et al 1997) according to in vitro tests – clinical significance unknown.	Usual dietary intakes likely to be safe. Concentrated extracts should be used with caution.
Meadowsweet	*Filipendula ulmaria*	In vitro and in vivo tests have identified anticoagulant activity (Liapina & Koval'chuk 1993) — clinical significance of these findings is unknown.	Suspend use of concentrated extracts 1 week before surgery.
Myrrh	*Commiphora molmol*	Guggul inhibits platelet aggregation in vitro and in a clinical study (Bordia & Chuttani 1979).	Suspend use of guggul preparations 1 week before surgery.
Policosanol		Doses of 10 mg/day and greater reduce platelet aggregation, according to clinical studies (Arruzazabala et al 2002, Castano et al 1999). Effect of 20 mg/day is similar to aspirin 100 mg stat.	Suspend use of doses 10 mg/day or greater 1 week before surgery.
Rosemary	*Rosmarinus officinalis*	Rosemary demonstrates antithrombotic activity in vitro and in vivo, possibly through inhibition of platelets. Clinical significance unknown.	Suspend use of concentrated extracts 1 week before surgery; however, clinical significance difficult to assess.
Shark cartilage		Substance displays anti-angiogenic properties, which could theoretically hinder healing.	Suspend use of supplement 1 week before surgery and until postoperative healing is complete (approx 6 weeks).
St John's wort	*Hypericum perforatum*	Use of herb for more than 2 weeks can induce pharmacokinetic interactions with CYP3A4 and P-gp substrates. This will result in reduced therapeutic responses to these drugs e.g. • alprazolam • cyclosporine • digoxin • midazolam • morphine • nortriptyline • warfarin	Use under professional supervision — if use is continued, drug doses may require modification. **Caution:** Withdrawal effects possible as SSRI-like activity is reduced and CYP and P-gp induction is removed — therapeutic failure of herb and possible drug toxicity.
Turmeric root	*Curcuma longa*	Curcumin inhibits platelet aggregation in vivo (Srivastava R et al 1985, 1986, Chen et al 2007) and in vitro (Srivastava KC 1989, Srivastava KC et al 1995, Jantan et al 2008). The anticoagulant effect of curcumin is weaker than that of aspirin — clinical significance unknown.	Usual dietary intakes likely to be safe. Suspend use of concentrated extracts 1 week before surgery.

Common name	Botanical name (where applicable)	Comments	Recommendation
Vitamin E	Alpha-tocopherol	Contradictory results have been obtained in clinical studies that have investigated whether vitamin E affects platelet aggregation or coagulation. A dose of 1200 IU/day (800 mg of D-alpha-tocopherol) taken for 28 days had no effects on platelet aggregation or coagulation, according to one clinical study (Morinobu et al 2002). Similarly, a second clinical study found the lower dose of 600 mg (900 IU) of RRR-alpha-tocopherol taken daily for 12 weeks did not alter coagulation activity (Kitagawa et al 1989). Alternatively, increased risk of gingival bleeding at doses of 50 mg/day was found by another study (Liede et al 1998).	Usual therapeutic doses are likely to be safe. Suspend use of high-dose supplements (> 1000 IU/day) 1 week before surgery; however, safety is difficult to assess.
Willow bark	*Salix* spp	Although it has been assumed that willow bark affects platelet aggregation owing to its salicylate content, one clinical study found that consumption of *Salicis cortex* (240 mg salicin daily) produced minimal effects on platelet aggregation (Krivoy et al 2001).	Use under observation but likely to be safe.

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Castano G et al. Effects of policosanol and pravastatin on lipid profile, platelet aggregation and endothelemia in older hypercholesterolemic patients. Int J Clin Pharmacol Res 19.4 (1999): 105–16.

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Harris WS et al. Fish oils in hypertriglyceridemia: a dose-response study. Am J Clin Nutr 51.3 (1990): 399–406.

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Kitagawa M, Mino M. Effects of elevated d-alpha(RRR)-tocopherol dosage in man. J Nutr Sci Vitaminol (Tokyo) 35.2 (1989): 133–42.

Krivoy N et al. Effect of salicis cortex extract on human platelet aggregation. Planta Med 67.3 (2001): 209–12.

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APPENDIX 6

CLINICAL USE AND SAFETY OF VITAMINS AND MINERALS

Clinical use and Safety of Vitamins						
Vitamin	**Australian and New Zealand RDI for adults (> 18 years)**	**Dose range used in practice**	**Major uses (oral or topical forms)**	**Cautions**	**Side effects**	**Toxicity**
A	Women: 700 μg Men: 900 μg	10,000–50,000 IU/day orally in divided doses Not recommended for more than 2 weeks without medical supervision	• Treating deficiency • Prevention of secondary deficiency (e.g. coeliac disease, cystic fibrosis, pancreatic disease) • Reducing severity of infectious diseases in children • Dermatology — many uses • Adjunct to chemotherapy • Slowing progression of retinitis pigmentosa • Osteoporosis • Anaemia	• Hypersensitivity • Pregnancy • Hypervitaminosis A • Retinoid analogue use • Lactation • Chronic renal failure or liver disease	**Early signs** • Dry rough skin and mucous membranes, desquamation • Coarse sparse hair, alopecia of eyebrows • Diplopia • Bone and joint pain **Later signs** • Irritability • Increased intracranial pressure and headache • Dizziness • Hepatotoxicity	• Cumulative toxicity if > 100,000 IU long term • Acute toxicity possible if > 2,000,000 IU • The recommended adult daily amount of vitamin A from all sources in 2500 IU. Taking more than 8000 IU a day during pregnancy may cause birth defects.
B_1 (thiamin)	Women: 1.1 mg Men: 1.2 mg	5–3000 mg	• Treating deficiency • Prevention of secondary deficiency (e.g. hyperemesis and malabsorption states) • Acute alcohol withdrawal • Alzheimer's dementia • Dysmenorrhoea • Congestive heart failure • Diabetes	• Hypersensitivity	Well tolerated	Non-toxic
B_2 (riboflavin)	Women: 1.1 mg (< 70 yrs: 1.3 mg) Men: 1.3 mg (>70 yrs: 1.6 mg)	10–400 mg/day	• Treating deficiency • Prevention of secondary deficiency (e.g. chronic diarrhoea, liver disease, chronic alcoholism) • Prevention of migraine headaches • Reducing incidence of both nuclear and cortical cataract • Wound healing • Pyridoxine metabolism • Breast cancer adjunct to Tamoxifen	• Hypersensitivity	Generally well tolerated, but rare side effects include diarrhoea and polyuria.	Non-toxic

B_3 (niacin)	Women: 11 mg Men: 12 mg	1500–2000 mg crystalline niacin or sustained-release forms daily	• Treating deficiency • Pellagra • Prevention of secondary deficiency (e.g. anorexia nervosa) • Hypercholesterolaemia and hypertriglyceridaemia • Syndrome X • Tryptophan deficiency • Diabetes	• Hypersensitivity • Diabetes • Peptic ulcer disease • Gout • Hepatitis • Liver function should be monitored and patients observed for symptoms of myopathy.	• Flushing is a common side effect (not with nicotinamide). Night-time administration, extended-release (ER) niacin or concurrent administration of aspirin can reduce these effects. • Palpitations, chills, pruritus, GIT upset and cutaneous tingling.	• Tachycardia, chills, sweating, shortness of breath, nausea, vomiting, myalgias, hepatotoxicity • ER niacin is considered the safest form.
B_5 (panto-thenic acid)	Women: 4 mg/day Men: 6 mg/day	200–300 mg/day	• Deficiency rare • Prevention of secondary deficiency (e.g. malabsorption syndrome, alcoholism, diabetes, OCP and IBD) • Enhanced wound healing • Hypercholesterolaemia • Prevention of NTD • Female alopecia		Well tolerated • Contact dermatitis from topical application	No toxicity level known
B_6 (pyridoxine)	Women: 1.3 mg (> 50 yrs: 1.5 mg) Men: 1.3 mg (> 50 yrs: 1.7 mg)	5–1200 mg/day	• Treating deficiency • Prevention of secondary deficiency (e.g. malabsorption syndromes, cancer, liver cirrhosis and alcoholism, hyperthyroidism) • Relieving symptoms of PMS and morning sickness • Leg cramps of pregnancy • Hyperhomocysteinaemia (often with folic acid and vitamin B_{12}) • Reducing thromboembolism • Improved outcomes after heart transplant • Reducing repeated febrile convulsions in children • Autism (with magnesium) • Stress	• Hypersensitivity • Long-term use of high-dose pyridoxine supplements (> 100 mg, although this level varies between individuals) should be used with caution.	• Nausea, vomiting, headache, paraesthesias, sleepiness and low serum folic acid levels have been reported. • If taken at night, may induce vivid dreams.	• Paraesthesia, hyperaesthesia, bone pain, muscle weakness, numbness and fasciculation most marked at the extremities • Unsteady gait, numbness of hands and feet, impaired tendon reflexes. • Excess doses of B_6 can cause degeneration of the dorsal root ganglia in the spinal cord, loss of myelination and degeneration of sensory fibres in the peripheral nerves.

Continued

Clinical use and Safety of Vitamins *continued*						
Vitamin	**Australian and New Zealand RDI for adults (> 18 years)**	**Dose range used in practice**	**Major uses (oral or topical forms)**	**Cautions**	**Side effects**	**Toxicity**
			• Cognitive performance/ Alzheimer's disease • Schizophrenia • Tardive dyskinesia • Parkinson's disease			• Dose and time frame at which toxicity occurs varies significantly between individuals. • Studies involving large populations found minimal or no toxicity with 100–150 mg/day over 5–10 years, whereas women self-medicating for PMS taking 117 ± 92 mg for 2.9 ± 1.9 years have reported increased incidence of peripheral neuropathy.
B_{12} (cobalamin)	Adult > 13 years: 2.4 μg/day	0.5–2000 mg/day	• Treating deficiency: primary deficiency (vegans and vegetarians, breast-fed infants of vegetarian mothers, elderly patients and alcoholics) • Prevention of secondary deficiency (e.g. atrophic gastritis, achlorhydria, pancreatic insufficiency, Crohn's disease, bacterial or parasitic infestations) • Pernicious anaemia • Hyperhomocysteinaemia (with B_6 and folate) • Cardiovascular protection • Prevention of NTD • Recurrent abortion • Depression • HIV infection • Cognitive impairment • Diabetic retinopathy • Sleep disorders • Tinnitus • Multiple sclerosis • Amyotrophic lateral sclerosis	• Hypersensitivity • Avoid in cases of altered cobalamin metabolism or deficiency associated with chronic cyanide intoxication.	None known	Well tolerated

Folate	Adults: 400 μg/day Up to 1 mg/day in deficiency states	1–30 mg/day	• Treating deficiency • Prevention of secondary deficiency (e.g. malabsorption syndromes such as coeliac and Crohn's disease, HIV infection), MTHFR gene polymorphism • Preconception care and pregnancy (prevention of neural tube defects) • Hyperhomocysteinaemia • Cardiovascular disease protection • Cognitive impairment • Anticonvulsant-induced folate deficiency • Depression • Schizophrenia • Reducing incidence of cancer • Periodontal disease • Vitiligo • Topical: periodontal disease	• Hypersensitivity • Use may mask B_{12} deficiency by correcting the apparent microcytic anaemia without altering the potential for or progression of neurological damage.	Doses > 5 mg/day: generalised urticaria, nausea, flatulence and bitter taste in the mouth, and some CNS activation in the form of irritability and excitability, altered sleep pattern.	Non-toxic
C	45 mg	250–12,000 mg/day orally in divided doses More used when administered IV	• Treating deficiency • Prevention of secondary deficiency (e.g. heavy smokers, achlorhydria, chronic diarrhoea, major surgery) • Treating iron deficiency anaemia (with iron) • Prevention and treatment of common URTI such as colds and influenza and mild allergic responses • Prevention and adjunctive treatment of cardiovascular disease and cancer • Management of diabetes and asthma • Atopy • Prevention of cataracts • Male infertility • Adjunct for haemodialysis patients	• Hypersensitivity • Increases iron, and decreases copper, absorption • Glucose-6-phosphate dehydrogenase deficiency • Haemochromatosis • Thalassaemia major • Sideroblastic anaemia • Renal impairment • Interacts with numerous laboratory tests (e.g. serum cholesterol and triglycerides and urinary oxalate; refer to monograph)	• None expected if < 3000–4000 mg/day, but this varies between individuals • Gastrointestinal upset: nausea, diarrhoea, flatulence, distension • Hyperoxaluria and renal stones now considered doubtful	Considered non-toxic

Continued

Clinical use and Safety of Vitamins *continued*						
Vitamin	**Australian and New Zealand RDI for adults (> 18 years)**	**Dose range used in practice**	**Major uses (oral or topical forms)**	**Cautions**	**Side effects**	**Toxicity**
			• Oral and topical forms used for various dermatological conditions (e.g. wound healing, photo-aged skin, prevention of sunburn (with vitamin E))			
D	Children & adults < 50 yrs: 200 IU/day Adults 51–70 yrs: 400 IU/day Adults > 70 yrs: 600 IU/day	400–300,000 IU/day	• Treating deficiency • Inadequate sun exposure or poor dietary intake • Prevention of secondary deficiency (e.g. malabsorption states) • Hypoparathyroidism (with calcium) • Hypophosphataemia (with phosphorus) • Prevention of bone fracture and osteoporosis (with calcium) • Hepatic and renal osteodystrophy • Scleroderma • Cancer • Diabetes • Prevention and treatment of infections • Depression • Multiple sclerosis • Lupus	• Hypersensitivity • Hypercalcaemia • Sarcoidosis • Hyperparathyroidism • SLE • Vitamin D toxicity • Pregnancy • Lactation • Renal failure • Use of cardiac glycosides, thiazide diuretics, calcium-channel blockers	• Not seen with doses < 2400 IU/day • Doses > 3800 IU: hypercalcaemia, soft tissue calcification • Fatigue, headache, nausea, vomiting, metallic taste, abdominal cramps, myalgia, tinnitus, arthralgia, constipation, polyuria, polydipsia	• Cumulative toxicity possible • Between 50,000 and 100,000 IU/day: signs of hypercalcaemia • 50,000–200,000 IU/day: nausea, vomiting, anorexia, polyuria, muscle pain • Calcification of soft tissue and organs, cardiac arrhythmias • Toxic levels cannot be obtained from sun exposure.

E	Women: 7 mg alpha-tocopherol Men: 10 mg alpha-tocopherol	50–3200 IU/day	• Treating deficiency • Prevention of secondary deficiency (e.g. malabsorption syndromes, cystic fibrosis) • Prevention of cardiovascular disease, certain cancers, ischaemic stroke in high-risk hypertensive patients, nitrate tolerance • Enhancing immune function in the elderly • Reducing incidence of common cold • Slowing progression of Alzheimer's dementia • Improving symptoms in PMS, dysmenorrhoea, menopause, intermittent claudication • Reducing pain in OA and RA • Cancer • Age-related macular degeneration • Huntington's disease • Treating some forms of male infertility • Oral and topical use for many dermatological states • Scar tissue • Prevention or treatment of many other conditions, such as exercise-induced tissue damage, some types of senile cataracts, epilepsy and fibromyalgia	• Hypersensitivity • People with impaired coagulation, inherited bleeding disorders, history of haemorrhagic stroke, vitamin K deficiency or at risk of pulmonary embolism or thrombophlebitis • Suspend use of supplements 1–2 weeks before major surgery.	• Adverse effects are dose-related and tend to occur only at very high doses (> 1200 IU/day) • Side effects include diarrhoea, flatulence, nausea and heart palpitations • Increased risk of bleeding if vitamin K deficiency present	Vitamin E is relatively non-toxic. Doses as high as 3200 mg/day have been used for 12 years without signs of toxicity.

Continued

CLINICAL USE AND SAFETY OF MINERALS *continued*

Mineral	Australian and New Zealand RDI for adults (> 18 years)	Dose range used in practice	Major uses (oral or topical forms)	Cautions	Side effects	Toxicity
Calcium	Adults: < 70 yrs: 1000 mg/day > 70 yrs: 1300 mg/day	100–2000 mg/day	• Treating deficiency • Prevention of secondary deficiency (e.g. achlorhydria and malabsorption syndromes), more common in elderly • Prevention of osteoporosis, pre-eclampsia, maintenance of bone density, colorectal cancer • Symptoms of PMS • Hypertension and hyperlipidaemia • Dyspepsia • Weight loss • Nephrolithiasis • Dry eye	• Hypersensitivity • Hyperparathyroidism • Hypercalcaemia • Renal impairment or kidney disease • Sarcoidosis or other granulomatous diseases only under medical supervision	Gastrointestinal discomfort, nausea, loss of appetite, constipation, flatulence, metallic taste, muscle weakness	• Increased serum calcium level may be associated with hypotonia, depression, lethargy and coma. • Prolonged hypercalcaemic state, especially if normal or elevated serum phosphate, can precipitate ectopic calcification of blood vessels, joints, gastric mucosa, cornea and renal tissue.
Chromium	Women: 25 μg Men: 35 μg	50–1000 μg	• Treating deficiency • Diabetes • Hypoglycaemia • Hyperlipidaemia • Obesity • Atypical depression • Polycystic ovary syndrome • Syndrome X • Exercise aid • Prevention of myocardial infarction	Hypersensitivity	• Irritability and insomnia have been reported with chromium yeast supplementation. • Chromium picolinate is well tolerated.	Chromium IV is used in industry and is highly toxic, whereas Cr III, which is used in supplements, is well tolerated.
Iodine	Adults: 150 μg/day	0.5–6 mg	• Treating deficiency • Secondary deficiency (high consumption of goitrogens combined with low iodine intake) • Preventing deficiency in high-risk groups including in utero, pregnancy, infancy • Prevention of ADHD • Fibrocystic breast disease • Breast cancer • Mastalgia	• Hypersensitivity • Thyroid conditions	Symptoms of iodine hypersensitivity are fever, painful joints, lymph node enlargement, eosinophilia, urticaria, angio-oedema, cutaneous and mucosal haemorrhage and fatal peri-arteritis.	• Chronic iodine toxicity when intake is > 2 mg/day. Symptoms: brassy taste in mouth, burning sensation in mouth and throat, increased salivation, gastric irritation, abdominal pain, nausea, vomiting and diarrhoea • Acneiform skin lesions, pulmonary oedema, depression • Chronic ingestion > 500 μg/day by children → increased thyroid size

Iron	Women: 19 to menopause: 18 mg Post-menopause: 8 mg Men: 8 mg	10–100 mg/day	• Treating deficiency • Prevention of secondary deficiency (e.g. menorrhagia, cystic fibrosis) • Unexplained fatigue without anaemia • Improving athletic performance • Pregnancy • Postpartum anaemia • Cognitive function • ADHD	• Hypersensitivity • Haemochromatosis • Haemosiderosis • Iron-loading anaemias (thalassaemia, sideroblastic anaemia) • Liquid iron preparations can discolour teeth (brush teeth after use).	• Gastrointestinal disturbances such as nausea, diarrhoea, constipation, heartburn, upper gastric discomfort • Preliminary evidence indicates iron may be implicated in the pathogenesis of various disease states. Therefore, supplementation is indicated only with demonstrated biological need.	Haemochromatosis can develop from long-term excessive intake Iron toxicity causes severe organ damage and death. The most pronounced effects are haemorrhagic necrosis of the gastrointestinal tract and liver damage.
Magnesium	Women: 310 mg > 30 yrs: 320 mg Men: 400 mg > 30 yrs: 420 mg	200–1200 mg/day	• Treating deficiency • Prevention of secondary deficiency (e.g. inflammatory bowel diseases, diabetes, hyperthyroidism, elevated cortisol) • Alleviating symptoms of coronary heart disease, reducing hypertension, reducing plasma lipid levels, reducing incidence of arrhythmias in congestive heart failure • Prevention of migraine headache, premenstrual headache, PMS, dysmenorrhoea, osteoporosis • ADHD, autism spectrum disorders • Kidney stone prevention • Asthma • Diabetes • Dyspepsia • Constipation • Chronic leg cramps • Leg cramps in pregnancy	• Hypersensitivity • Renal failure and heart block (unless pacemaker present)	**Most common** • Diarrhoea and gastric irritation; usually not seen at doses < 350 mg/day (elemental) • Doses of inorganic magnesium > 350 mg/day may be associated with adverse effects. Dividing doses will maximise bioavailability and reduce side effects. • Overuse of magnesium hydroxide or magnesium sulfate may cause deficiencies of other minerals or lead to toxicity. **Other side effects** Decreased heart rate, hypotension, muscle weakness	Most commonly seen in patients with renal insufficiency. Symptoms: muscle weakness, sedation, ECG changes, confusion, hypotension

Continued

CLINICAL USE AND SAFETY OF MINERALS *continued*

Mineral	Australian and New Zealand RDI for adults (> 18 years)	Dose range used in practice	Major uses (oral or topical forms)	Cautions	Side effects	Toxicity
Selenium	Women: 60 μg Men: 70 μg	80–200 μg/day	• Treating deficiency • Prevention of secondary deficiency (e.g. cirrhosis, malabsorption syndromes, cystic fibrosis, coeliac, disease, HIV infection) • Reducing total cancer incidence and mortality (especially lung, colorectal and prostate cancers), adjunctive treatment • HIV infection • Cardiovascular disease • Autoimmune thyroiditis • Diabetes • Symptoms of RA, asthma • Male infertility • Immune enhancement • Anxiety and depression • Reducing morbidity in preterm infants	• Hypersensitivity • NHMRC upper level of intake is 400 μg/day	• Nausea, vomiting, nail changes, irritability, fatigue • Organic form of selenium found in high-selenium yeast is less toxic and safer than other forms.	Long-term use of excessive doses (> 1000 μg/day) can produce fatigue, depression, arthritis, hair or finger-nail loss, garlicky breath or body odour, gastrointestinal disorders and irritability.
Zinc	Women: 8 mg/day Men: 14 mg/day	25–200 mg/day	• Treating deficiency • Prevention of secondary deficiency (e.g. cirrhosis, malabsorption syndromes, severe burns, major surgery) • Treating the common cold and reducing symptoms • Age-related macular degeneration • Diabetes • Enhancing wound healing (e.g. leg ulcers)	• Hypersensitivity	Mild gastrointestinal upset at doses of 50–150 mg/day	• Single doses of 225–450 mg usually induce vomiting • Nausea, vomiting, diarrhoea, fever and lethargy have been observed after ingestion of 4–8 g. • Doses ranging from 100 to 150 mg/day interfere with copper metabolism and cause hypocupraemia, red blood cell microcytosis, and neutropenia if used long term.

			• Decreasing relapse rates in Crohn's disease • Decreasing incidence of pneumonia • Arterial and venous leg ulcers • Male infertility • Impotence • ADHD • Depression • Diarrhoea • Anorexia nervosa • Tinnitus • Warts • Acne vulgaris • Topical: herpes simplex infection			

Note

Mutivitamins. Overall, acute toxicity is unlikely with combination vitamin supplements unless huge amounts have been ingested. In the case of toxicity or side-effects, signs and symptoms will relate to the individual nutrient ingested. In general, gastrointestinal symptoms such as discomfort, nausea and diarrhoea are the most frequent adverse effects.

Special care. Of all the nutrients listed, extra special care must be taken when supplementing with vitamins A and D and the mineral iron. The forms of selenium and niacin used in practice also have a major influence on their safety profile and should be taken into consideration.

RDI. For more details regarding RDI for specific age groups: www.nhmrc.gov.au/publications/synopses/n35syn.htm

APPENDIX 7

EVIDENCE BASE FOR PHYSIOLOGICAL ACTIVITIES OF HERBS AND SUPPLEMENTS

Evidence codes

AS Animal studies

CT Clinical trial

EP Based on epidemiological studies

IV In vitro studies

PH Based on known pharmacological activity of constituents

TH Theoretical

TU Traditional use

Assumptions made when collating the information for this table

- Information is compiled from the 130 monographs included in this book.
- All information refers to oral dose forms unless otherwise specified.
- Information listed here is correct at the time of writing; however, because of the ever-expanding knowledge base in this area, new research is constantly being published.
- Not all actions referred to in the text are covered; see monographs for more detail.

Major actions (known or suspected)	Herb/Nutrient	Evidence	Comments
Adaptogenic			
	Brahmi	IV, AS	
	Ginseng — Korean	AS, CT	Thought to influence hypothalamic–pituitary–adrenal axis.
	Ginseng — Siberian	IV, AS, CT	Appears to alter the levels of different neurotransmitters and hormones involved in the stress response chiefly at HPA axis.
	Rhodiola	AS, CT	Found to prevent catecholamine release.
	Shatavari	TU, AS	
	Tyrosine	CT	Appears to enhance release of catecholamines during stress.
	Withania	AS	Suppresses stress-induced increases in dopamine receptors and acts as a GABA-mimetic agent; ability to reduce adrenal weight and plasma cortisol levels.

Major actions (known or suspected)	Herb/Nutrient	Evidence	Comments
Analgesic			
	Brahmi	AS	Antinociceptive activity identified when used in combination with other herbs.
	Chondroitin	CT	Musculoskeletal pain.
	Clove oil	AS, CT	Effects due to the eugenol, beta-caryophyllene component; clinical trials used tiger balm.
	Dandelion (root)	AS	Mild effects reported.
	Devil's claw	CT, AS	Opioid system involved in the antinociceptive effects.
	Eucalyptus	AS	Central and peripheral effects attributed to monoterpene components.
	Evening primrose oil	PH	
	Fenugreek	AS	Antinociceptive activity identified.
	Feverfew	AS, CT	Inhibits prostaglandin production and acts at nociceptors.
	Ginger	CT	Inhibits prostaglandin and thromboxane production and topically depletes substance P.
	Ginseng — Korean	AS	Potentiates opioid-induced analgesia.
	Glucosamine	CT	Musculoskeletal pain — effects seen in osteoarthritis.
	Kava kava	IV, AS	Local anaesthetic.
	Lemon balm	IV, AS	High doses.
	Meadowsweet	TH	Based on its high salicylate content.
	Noni	AS	Opioid-like properties, dose-dependent analgesic properties.
	Peppermint oil	CT	Observed for oil applied topically.
	St John's wort	IV, AS	Binds opioid receptors and modulates COX-2 expression.
	SAMe	CT	Musculoskeletal pain — effects seen in osteoarthritis (not prostaglandin mediated).
	Shark cartilage	AS	Multiple mechanisms.
	Stinging nettle	CT	Probably due to counter-irritant effect.
	Vitamin E	CT	Most likely mediated via inhibitory effects on COX-2 and 5-lipooxygenase.
	Willowbark	CT	Musculoskeletal pain.
Antacid			
	Magnesium	TU	
	Meadowsweet	TU	
Anthelmintic			
	Thyme	IV	Thymol possesses antihelmintic activity.
Anti-allergic			
	Adhatoda	IV, AS	Asicine and vasicinone possess bronchodilatory activity and inhibit allergen-induced bronchial obstruction, with effects comparable to those of sodium cromoglycate.
	Albizia	IV, AS	Significant mast-cell-stabilisation effects, similar to those of sodium cromoglycate. Recent comparative study found albizia leaf, albizia stem and bark, and disodium chromoglycate to be equally potent on mast cell stabilisation.

Continued

Major actions (known or suspected)	Herb/Nutrient	Evidence	Comments
	Baical skullcap	IV, AS	Baicalein has been shown to inhibit IgE antibody-mediated immediate and late phase allergic reactions; inhibited IgE-mediated TNF-alpha and IL-6 production from mast cells; suppressed leukotriene C4 release by polymorphonuclear leucocytes. Baicalin 5-10-fold more potent than azelastine.
	Brahmi	IV	Potent mast-cell-stabilising activity (methanolic fraction) comparable to that of disodium cromoglycate.
	Clove oil	IV, AS	Inhibits histamine release.
	Feverfew	IV, AS	Inhibits histamine release (different mechanism to cromoglycate); constituent parthenolide significantly inhibits IgE-antigen-induced mast cell degranulation.
	Ginger	IV	Dose-dependent inhibition of drug-induced histamine release.
	Ginseng — Korean	IV	Stabilises cell membrane.
	Ginseng — Siberian	IV	Inhibits histamine release, tumour necrosis factor-alpha and IL-6.
	Hops	AS	Inhibits histamine release.
	Licorice	AS	Relieves IgE-induced allergic reactions.
	Peppermint	IV, AS	Inhibits histamine release.
	Perilla	IV, AS, CT	Inhibits histamine release, down-regulates Th2-type cytokine production, suppresses IgE and IgG antibodies and IL-4, IL-5 and IL-10.
	Probiotics	CT	Reduces antigen transport through the intestinal mucosa.
	Quercetin	IV, AS	Stabilises mast cells, neutrophils and basophils.
	St Mary's thistle	IV, AS	Mast-cell stabilisation.
	Stinging nettle	CT	Freeze-dried preparation showed activity.
	Vitamin C	CT	Reduces histamine levels.
Anti-anxiety/anxiolytic			
	Baical skullcap	IV, AS	Certain constituents bind with the benzodiazepine-binding site of the GABA-A receptor.
	Chamomile	AS	Binds benzodiazepine receptors.
	Ginger	AS	In combination with ginkgo biloba.
	Ginseng — Korean	IV, AS	Regulates GABA-A receptors in vitro.
	Kava kava	CT	Various mechanisms.
	L-Lysine	CT	5-HT_4 receptor antagonist and benzodiazepine receptor agonist.
	Lavender oil	AS, CT	Induces relaxation and sedation.
	Lemon balm	AS, CT	Eugenol and citronellol bind to GABA-A receptors and increase the affinity of GABA to receptors.
	Passionflower	AS, CT	Unknown mechanism — possibly acts via GABA.
	Quercetin	AS	Mechanisms unknown.
	St John's wort	IV, AS	Various mechanisms — possibly acts via GABA.
	Sage oil	IV	Compounds in methanolic extract have affinity for benzodiazepine receptors.

Major actions (known or suspected)	Herb/Nutrient	Evidence	Comments
	Valerian	IV, AS, CT	Stimulates the release of GABA, inhibits GABA reuptake and may have an effect at GABA receptors; low-dose valerian (100 mg) reduces situational anxiety without causing sedation.
	Withania	AS, CT	Exerted by constituent glycowithanolides.
Anti-atherogenic — See listing under Lipid-lowering			
Antibacterial — See listing under Antimicrobial			
Anti-catarrhal			
	Eucalyptus	CT	Decreased nasal congestion
	Horseradish	TU	Eliminates respiratory tract catarrh
Anticancer (e.g. antimutagenic, antineoplastic and/or anti-angiogenic activity has been identified)			
	Andrographis	IV	Increases apoptosis of prostate cancer cells; decreased proliferation of human cancer cells.
	Astragalus	IV, AS, CT	Tested in combination with other herbs.
	Baical skullcap	IV, AS	Baicalein, baicalin and wogonin shown to induce apoptosis, inhibit proliferation, prevent metastases and inhibit angiogenesis; *S. baicalensis* demonstrated dose-dependent inhibition of squamous cell carcinoma, breast cancer, hepatocellular carcinoma, prostate carcinoma and colon cancer cell lines.
	Bilberry	IV, AS	Anticarcinogenic and anti-angiogenic activity; inhibition of nuclear factor-kappa B activation pathway.
	Chamomile	IV, AS	Apigenin has been shown to inhibit carcinogenesis in a variety of experimental models.
	Cinnamon	IV	Antitumour activity.
	Cranberry	IV	Due to proanthocyanidins.
	Creatine	AS	Antitumour.
	Clove oil	IV	Demonstrated anticancer apoptosis activity constituent eugenol.
	Dandelion	IV	Anti-angiogenic.
	Dong quai	IV	Anti-tumour effects.
	Dunaliella salina	IV	Antiproliferative.
	Echinacea	IV	Induces apoptosis.
	Fenugreek	IV, AS	Antineoplastic; induced apoptosis in vitro to breast, pancreatic and prostate cancer.
	Flaxseed oil	PH	ALA demonstrated to inhibit tumour progression.
	Garlic	IV, AS	Various mechanisms; antineoplastic in breast, prostate, endometrial, stomach and colon cancer.
	Ginkgo	IV, AS	Antioxidant, anti-angiogenic and gene-regulating activity.
	Ginseng — Korean	IV, AS	Antitumour, antimetastatic, induces apoptosis and is radioprotective.
	Goldenrod	IV, AS	Antineoplastic activity demonstrated against prostate, breast, small-cell lung carcinoma and melanoma cancer cell lines in vitro; prostate cancer cell in vivo.
	Goldenseal	IV, AS	Demonstrated for the berberine constituent.
	Grapeseed extract	IV, CT	Suppresses tumour growth and has cytotoxic activity against a range of cancer cells, including breast, lung, prostate, and gastric adenoma cells.

Continued

Major actions (known or suspected)	Herb/Nutrient	Evidence	Comments
	Green tea	IV, EP	Reduction in proliferation, increase in apoptosis and possible anti-angiogenic properties identified; supported by epidemiological studies.
	Horseradish	PH	Antitumour.
	Lavender	IV, AS, PH	Preliminary evidence of activity for several constituents.
	Lavender oil	IV, AS	Antineoplastic in cancer of the colon, liver, lung, breast, pancreas, prostate, as well as melanoma.
	Licorice	IV, AS	Antitumour, anti-angiogenic, cell-cycle arrest and induces apoptosis.
	Lutein	CT	Possibly endometrial, lung, breast, bowel.
	Mullein	IV	Antitumour.
	Noni	IV, AS	Antitumour, antiproliferative and induces apoptosis.
	Oats		Anticytotoxic, antimutagenic, antitumourogenic.
	Perilla	IV, AS	Multiple mechanisms involved.
	Quercetin	IV, AS	Multiple mechanisms involved.
	Red clover	IV, AS, CT	Antimutagenic, antiproliferative and anti-angiogenic in vitro as well as protecting against chemical-induced DNA damage.
	Red yeast rice	ES	Antitumour.
	Rhodiola	IV, AS	Animutagenic, cytostatis, antiproliferative and antimetastatic.
	St John's wort	IV, AS	Selective photosensitisation of tumour cells; antineoplastic, anticarcinogenic, antiproliferant, proapoptotic, antiinvasive and antimetastatic effects.
	St Mary's thistle	IV, AS	Anti-angiogenic and antitumour.
	Saw palmetto	IV	Prostate cancer cell lines.
	Schisandra	IV	Anticancer activity demonstrated against leukaemia, lung and hepatocellular cancer cells in vitro.
	Shark cartilage	IV, AS	Anti-angiogenic and antitumour.
	Shatavari	AS	
	Soy	IV, ES AS	Multiple mechanisms attributed to phyto-oestrogen and isoflavone content. Activity shown against breast and prostate cancers.
	Turmeric	IV, AS, CT	Promotes apoptosis, reduces proliferation, reduces angiogenesis and metastases.
	Vitamin A	CT	Stimulates epithelial cell differentiation, preventing the proliferation of dedifferentiated or undifferentiated carcinoma cells in skin, breast, liver, colon, cervical, prostate, oral, pharyngeal, oesophageal and lung carcinomas.
	Vitamin B_6	IV	Antitumour on cell lines including breast and pituitary cells.
	Vitamin D	IV	
	Withania	IV, AS	Antineoplastic, anti-angiogenic and enhances apoptosis.
Chemoprotection			
	Beta-carotene	EP, AS	Effect associated with 'natural' beta-carotene and natural sources. Mechanisms proposed include antioxidant activity, stimulation of gap junction communication, inhibition of cell proliferation and oncogene expression.

Major actions (known or suspected)	Herb/Nutrient	Evidence	Comments
	Calcium	CT	Prevention of colorectal cancer and recurrence of adenomatous polyps.
	Celery	AS	May reduce incidence of stomach, colon, liver and lung cancer
	Dunaliella salina	IV	Effects associated with 'natural' beta-carotene component.
	Echinacea	AS	Reduces tumour incidence.
	Feverfew	IV, CT	Attributed to constituent parthenolide, which inhibits cell cycle, promotes cell differentiation and induces apoptosis; breast, cervical, prostate cancers.
	Fish oils	IV, AS	Demonstrated actions include suppression of neoplastic transformation, cell growth inhibition, enhanced apoptosis and anti-angiogenicity; especially breast, prostate and colorectal cancers.
	Flaxseed oil	CT	Increased levels of ALA associated with reduced risk of breast cancer.
	Folate	EP, AS, CT	Especially cervix, colorectal, lung, oesophagus, brain, pancreas and breast cancers.
	Garlic	IV, AS	Various mechanisms.
	Ginger	IV, AS	Antitumour properties partly due to antioxidant and anti-inflammatory effect; breast, ovarian, gastric and pancreatic cancers.
	Ginkgo	AS	
	Ginseng — Korean	IV, AS, CT	Various mechanisms.
	Guarana	AS	Reduces cellular proliferation of preneoplastic cells.
	Hops	IV	Component chalcone, xanthohumol prevents angiogenesis in vivo.
	Horse chestnut	AS, IV	Inhibits cell proliferation and induces apoptosis.
	Lutein and zeaxanthin	EP	Various cancers.
	Lycopene	IV, AS, CT	Thought to inhibit proliferation of cancer cells by initiating cell-cycle arrest and apoptosis; especially prostate, stomach and cervical cancers.
	Olive	IV	Anticarcinogenic, antimetastatic, antimutagenic and anti-angiogenic.
	Prebiotics	IV, AS	Anti-cancer effects.
	Probiotics	IV, AS, CT	Antimutagenic, anticarcinogenic (e.g. nitrosamines), immune enhancing.
	Pygeum	IV, AS	Regulation of cancer cell growth in vitro and in vivo; against prostate cancer.
	Rosemary	IV, AS, TU	
	St Mary's thistle	AS, IV	
	Selenium	CT, EP	Significantly reduces total cancer mortality, total cancer incidence and incidence of lung, colorectal and prostate cancers.
	Stinging nettle	IV, CT	Antiproliferative in prostate cells.
	Turmeric	AS, CT	Against skin, stomach, colon, prostate, breast and oral cancer.

Continued

Major actions (known or suspected)	Herb/Nutrient	Evidence	Comments
	Vitamin A	IV, AS	Deficiency can induce metaplastic changes to epithelial cells; retinoic acid thought to act as inhibitor of carcinogenesis.
	Vitamin B_3	IV, AS	Dietary niacin status potentially affects DNA repair, genomic stability and immune function influencing cancer risk.
	Vitamin C	EP, IV	Mechanisms largely unknown.
	Vitamin D	EP, CT	Demonstrated reduction of incidence of all cancers.
	Vitamin E	EP	
	Withania	IV, AS	Multiple mechanisms.
	Zinc	EP	
Antifibrotic			
	Baical skullcap	IV, AS	In combination; chemopreventive role in the development of hepatocellular carcinoma.
	Ginger	CT	
	St Mary's thistle	AS	Against liver fibrosis.
Radioprotective			
	Ginseng — Korean	IV, AS	
	Hawthorn	IV	
	Peppermint	AS	Exerted through antioxidant and free-radical scavenging activities.
Anticoagulant — See listing under Blood thinning			
Anticonvulsant			
	Albizia	AS	
	Baical skullcap		Constituent wogonin exhibits anticonvulsive effects mediated by GABA.
	Devil's claw	AS	Anticonvulsive action through GABAergic neurotransmission.
	Ginseng — Korean	AS	
	Lavender oil	AS	
	Passionflower	IV	Action through GABAergic and opioid pathways.
	Withania	AS	Likely due to GABA-A modulation.
Antidepressant/neurotransmitter effects			
	Albizia	AS	Influences GABA, serotonin and dopamine levels.
	Brahmi	AS	Mechanism unknown.
	Chromium	AS	Various mechanisms.
	Fish oil	CT	Various mechanisms.
	Folate	CT	Effectiveness may be restricted to those patients with an existing deficiency.
	Ginkgo biloba	IV, AS	May inhibit MAO-A; increases uptake of serotonin; direct and indirect cholinergic activity; competitive antagonist for GABA-A receptors; moderation of corticosterone levels.
	Licorice	IV	Inhibits serotonin reuptake; effect upon norepinephrine and dopamine.

Major actions (known or suspected)	Herb/Nutrient	Evidence	Comments
	Perilla	AS	Mechanism unknown — possibly through cell proliferation in the hippocampus.
	Rhodiola	IV	Various mechanisms.
	St John's wort	CT	Various mechanisms.
	SAMe	CT	Various mechanisms.
	Selenium	CT	Low dietary intakes of selenium have been linked with greater incidence of anxiety, depression and tiredness.
	Shatavari	IV	Thought to be mediated via serotonergic and noradrenergic systems and antioxidant activities.
	Tyrosine	CT	Precursor to neurotransmitters.
	Valerian	AS	
	Vitamin B_1 (thiamin)		Involved in neurotransmitter synthesis.
	Vitamin B_6 (pyridoxine)	TH	Supplementation can elevate GABA and serotonin levels by increasing production.
	Vitamin C	PH	Cofactor required for the biosynthesis of noradrenaline from dopamine and hydroxylation of tryptophan to serotonin; also a modulator of glutaminergic, cholinergic and GABAergic transmission.
	Withania	AS	Effects comparable to those of imipramine.
	Zinc	EP, CT	Inverse relationship between serum zinc and depression.
Antidiarrhoeal			
	Bilberry	TH, PH	Due to tannins and astringent activity.
	Colostrum	CT	Effective against some forms of infectious diarrhoea.
	Goldenseal	IV, AS, CT	Due to berberine constituent.
	Probiotics	CT	Includes infant, travellers', infectious, acute and antibiotic-induced diarrhoea.
	Psyllium	CT	
	Raspberry	TU, PH	Due to tannins and astringent activity.
	Sage	TU, PH	Due to tannins and astringent activity.
	Shatavari	AS	Similar to the drug loperamide.
	Thyme	TU, PH	Due to tannins and astringent activity.
Anti-emetic			
	Bacial skullcap	AS, CT	
	Ginger	AS, CT	Multiple mechanisms.
	Peppermint oil	CT	Peppermint oil inhalation.
	Shatavari	CT	Promotes gastric emptying.
Antifibrotic — See listing under Anticancer			
Antifungal — See listing under Antimicrobial			
Antihypertensive/hypotensive			
	Andrographis	AS	Involves adrenoceptors, autonomic ganglia receptors and a reduction in circulating angiotensin-converting enzyme. Constituent 14-deoxy-11, 12-didehydroandrographolide found to induce relaxation of vascular smooth muscle and decrease heart rate.
	Astragalus	AS	Intravenous administration in rats.

Continued

Major actions (known or suspected)	Herb/Nutrient	Evidence	Comments
	Baical skullcap	AS	Mechanism unknown; may be due to peripheral vasodilation, inhibition of lipoxygenase and reduced production and release of arachadonic acid.
	Calcium	CT	Results variable, possibly in 'salt sensitive' hypertension. Mechanisms speculated to include reduced cellular calcium influx, inhibition of vasoconstriction, reduced activity of renin-angiotensin system and improved Na/K.
	Chromium	AS	Effect on renin-angiotensin system.
	Coenzyme Q10	CT, CT	Mechanism unknown but may reduce total peripheral resistance.
	Evening primrose oil	CT	Effect may be mediated through prostaglandin metabolism.
	Fenugreek	IV	
	Fish oils	CT	Appears dose-dependent and DHA may have greater effect than EPA.
	Flaxseed oil	PH	Mechanisms unknown.
	Garlic	AS, CT	Renin–angiotensin and NO may be involved.
	Ginger	AS	Via stimulation of muscarinic receptors and blockade of calcium channels.
	Ginseng — Korean	IV, AS, CT	May be attributed to an angiotensin-converting-enzyme inhibitory effect.
	Green tea	AS, IV	Angiotensin-converting-enzyme inhibition.
	Hawthorn	TU, IV, AS	Mechanism unknown, but may reduce total peripheral resistance.
	Magnesium	CT	Affects NO release and vascular tone.
	Oats	CT	Mechanism unknown.
	Olive oil and Olive leaf	IV, AS	Mechanism unknown.
	Quercetin	AS, CT	Decreases blood pressure and restores endothelial function.
	Stinging nettle	AS	Administered IV; mechanism attributed in part to negative inotropic activity and vasodilatory effect.
	Vitamin C	CT	Results overall positive.
	Vitamin E	CT	Modulates vascular function, possibly via NO; may also normalise genetic endothelial dysfunction.
	Zinc	CT	Supplementation consistently reduced duration and volume of diarrhoea.
Anti-inflammatory			
	Adhatoda		Alkaloid fraction (deoxyvasicinone [22] naturally occurring quinazolinone alkaloid) shown to be equivalent to hydrocortisone in one study.
	Aloe	AS	Aloe vera gel reduces oxidation of arachidonic acid, thereby reducing prostaglandin synthesis and inflammation.
	Andrographis	IV	May involve promotion of ACTH and enhancement of adrenocortical function. Antioxidant mechanisms are likely to contribute to anti-inflammatory effect.

Major actions (known or suspected)	Herb/Nutrient	Evidence	Comments
	Baical skullcap	IV, AS	May bind a variety of chemokines and limit their biological function; inhibits COX-2, PGE_2, 5-lipoxygenase, suppresses iNOS protein expression and NO production.
	Bilberry	AS	Reduces oedema.
	Bitter melon	IV	Suppresses LPS-induced TNF alpha production.
	Black cohosh	AS	
	Brahmi	IV	Various mechanisms; inhibition of COX-2, 5-LOX and down-regulation of TNF-alpha; inhibition of PGE_2, histamine, serotonin and bradykinin release.
	Calendula	IV, AS	Reduces oedema
	Celery	AS	Mechanism unknown.
	Chamomile	AS	Most research uses topical application.
	Chondroitin	IV	Regulates gene expression and synthesis of NO and PGE_2; inhibition of NF-kB nuclear translocation; increases antioxidant enzymes.
	Chromium	AS	Reduces pro-inflammatory cytokines TNF-alpha, IL-6 and CRP.
	Cinnamon	IV, AS	
	Clove oil	AS	Due to the eugenol, beta-caryophyllene component, inhibits prostaglandin synthesis through COX-1 & -2 and inhibits leukotrienes release.
	Cocoa	PH	
	Damiana	AS	Mechanism unknown.
	Dandelion (root)	AS	Mild activity.
	Devil's claw	IV, AS, CT	Various mechanisms may be due in part to antioxidant activity. Constituent harpagoside shown to suppress COX-2 and iNOS.
	Dong quai	AS	
	Echinacea	IV, AS	Multiple constituents; multiple mechanisms including Inhibits COX-1 and COX-2.
	Elder	IV	Inhibited activation of nuclear factor kappaB and phosphatidylinositol 3-kinase.
	Eucalyptus	AS, CT	Inhibition of inflammatory markers such as TNF-alpha, COX enzymes, 5-lipoxygenase and other leukotrienes.
	Evening primrose oil	AS, CT	Precursor to PGE_1.
	Fenugreek	AS	Mechanism unknown.
	Feverfew	IV	Inhibition of COX enzymes, lipoxygenase, platelet-activating factor, cytokines and NO.
	Fish oils	AS, CT	Chiefly prostaglandin mediated.
	Flaxseed oil	AS	Attributed to metabolites of ALA in formation of anti-inflammatory eicosanoids and modulation of cytokine production.
	Garlic	IV, AS, CT	Mechanisms identified inhibiting TN-kappa, modification of COX activity and suppression of iNOS and NO.
	Gentian	IV	
	Ginger	IV, AS, CT	Various mechanisms.
	Ginkgo biloba	IV, AS	Demonstrated reduced PGE_2, TNF-alpha and NO production.

Continued

Major actions (known or suspected)	Herb/Nutrient	Evidence	Comments
	Ginseng — Korean	AS	Ginsenosides suppress NF-kappa-B and COX-2.
	Ginseng — Siberian	IV	Suppresses NO production and iNOS gene expression.
	Glucosamine	IV	Altering production of TNF-alpha, interleukins, prostaglandins, NO and cytokines.
	Goldenrod	AS	Mechanism unknown
	Goldenseal	IV, AS	Due to the berberine content.
	Grapeseed extract	IV, AS	Demonstrated inhibitory activity against COX-1 and -2, and 5-lipoxygenase.
	Green tea		
	Hawthorn	IV, AS	Chiefly due to the flavonoid constituents.
	Honey	CT	Topical use.
	Hops	IV, CT	Reduces NO and inhibits production of PGE_2.
	Horse chestnut	IV, AS	
	Lavender		
	Lemon balm	IV	Rosmarinic acid anti-inflammatory; eugenol inhibits COX-1 and -2.
	Licorice	PH, IV, AS	Largely mediated by cortisol, although other mechanisms likely to exist.
	Meadowsweet	TH	High salicylate content.
	Myrrh	AS	Activity exhibited in resin and oil.
	New Zealand green-lipped mussel	IV, AS, CT	Possibly via effects on prostaglandins and leukotrienes.
	Noni	IV, CT	Demonstrated reduced superoxide radicals and lipid peroxidases.
	Olive oil and Olive leaf	PH, CT	Inhibits platelet aggregation, lipoxygenase, eicosanoid production and modulates C-reactive protein.
	Perilla	IV, CT	Refined oil and seed extract modulates prostaglandin, leukotriene synthesis and inhibits 5-lipoxygenase.
	Probiotics	IV, CT	Multiple mechanisms specific to strains including down-regulation of proinflammatory cytokines.
	Pygeum	PH, IV	Modulation of prostaglandins, leukotrienes and other 5-lipoxygenase metabolites.
	Quercetin	IV, AS	Modulated neutrophil function, prostanoid synthesis, cytokine production and iNOS expression via inhibition of NF-Kappa-B pathway.
	Raspberry	TU, PH	Topically, due to tannins.
	Red yeast rice	CT	Various mechanisms; significant reduction of CRP.
	Rosemary	IV	Possibly via effects on prostaglandins and leukotrienes.
	St John's wort	IV, AS	Various mechanisms.
	St Mary's thistle	IV, AS	Various mechanisms.
	SAMe	IV, CT	Not prostaglandin mediated.
	Saw palmetto	IV	Dual inhibitor of the cyclo-oxygenase and 5-lipoxygenase pathways and decreases COX expression.
	Schisandra	IV	Demonstrated inhibition of NO production, prostaglandin E(2), COX-2, iNOS, nuclear factor-kappaB and leukotrienes in vitro.

Major actions (known or suspected)	Herb/Nutrient	Evidence	Comments
	Selenium	IV, AS	Possibly via effects on prostaglandins, cytokines and leukotrienes.
	Shark cartilage	AS	Multiple mechanisms including inhibition of IL-1 induced PGE (2) synthesis and down-regulation of vascular endothelial growth factor.
	Slippery elm	TU, TH	High mucilage content; soothes irritated and inflamed tissues.
	Stinging nettle	IV, EP, CT	Various mechanisms.
	Tea tree oil	AS	
	Thyme	IV	Constituent thymol.
	Turmeric	AS	Activities exerted through multiple mechanisms.
	Vitamin E		Inhibits phospholipase A2 activity, suppressing arachidonic acid metabolism.
	Wild yam	TU	
	Willowbark	CT	Chiefly due to salicylate content.
	Withania	IV, CT	Suppresses pro-inflammatory mediators in vitro and found to ESR in clinical trial.
Anti-lithic			
	Shatavari	AS	Reduced elevated urinary concentrations of calcium, oxalate and phosphate and increased urinary concentration of magnesium.
	Tribulus	IV, AS	Reduced urinary oxalate; in human studies activity attributed to diuretic action.
Antimicrobial			
	Albizia	IV, AS	Antifungal and antibacterial.
	Aloe vera	IV	Activity against *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Streptococcus pyogenes*, *Staphylococcus aureus*, *Escherichia coli, Shigella flexneri*, methicillin-resistant *Staphylococcus aureus, Enterobacter cloacae* and *Enterococcus bovis.*
	Andrographis	IV	Demonstrated significant antimicrobial and antifungal activity in vitro when compared to standard antibiotics.
	Baical skullcap	IV	Antibacterial, antiviral and antifungal. Antibacterial against peridontopathogens, *Salmonella typhimurium.*
	Bitter melon	IV	Antibacterial and antiviral — activity against *E. coli*, *Salmonella paratyphi*, *Shigella dysenterae* and *Streptomyces griseus*, *Helicobacter pylori*, *Mycobacterium tuberculosis.* Antiprotozoal activity against *Entamoeba histolytica.*
	Brahmi	IV	Significantly inhibited *H. pylori.*
	Calendula	IV	Antibacterial, antiviral and antifungal.
	Chamomile	IV	Bactericidal and fungicidal activities against Gram-positive bacteria (*Bacillus subtilis*, *Staphylococcus aureus*) and *Candida albicans*, *Escherichia coli*, *Streptococcus mutans.*
	Chitosan	AS	May exert antibacterial activity against *Bifidobacterium* and *Lactobacillus* spp; oral antibacterial activity against *Streptococcus mutans* and inhibits adhesion of *Candida albicans.* Exhibits antifungal activity.

Continued

Major actions (known or suspected)	Herb/Nutrient	Evidence	Comments
	Cinnamon	IV	Broad-spectrum antibacterial and antifungal activities. *Bacillus subtilis, Escherichia coli, Saccharomyes cerevisiae, Candida albicans*, *L. monocytogenes, Salmonella enterica* and *Helicobacter pylori;* antibiotic-resistant *E. coli* and *Staphylococcus aureus.*
	Clove oil	IV, AS	Demonstrated activity against Gram-negative anaerobic periodontal oral pathogens, including *Porphyromonas gingivalis*, *Prevotella intermedia*; also *Bacillus subtilis*, *Listeria monocytogenes*, *Salmonella enterica*, *Escherichia coli* and *Saccharomyces cerevisiae*; hepatitis C virus protease; human cytomegalovirus, herpes simplex virus 1; *Candida albicans, Helicobacter pylori and Staphlococcus epidermidis*.
	Cloves	IV	Antibacterial, antifungal and antiviral.
	Colostrum	IV	Hyperimmune colostrums exhibit widespread antimicrobial activity, including *Shigella flexneri, Escherichia coli, Clostridium difficile, Streptococcus mutans, Cryptosporidium parvum* and *Helicobacter pylori*.
	Cranberry	IV, AS, CT	Bacteriostatic — reduced adhesion of *Escherichia coli,* Gram-negative and Gram-positive bacteria to uroepithelial tissues, and of *Helicobacter pylori* to human gastrointestinal cells.
	Dunaliella salina	IV	Antibacterial.
	Echinacea	IV	Antiviral, antifungal and antiparasitic.
	Eucalyptus	IV, CT	Activity against *Pseudomonas aeruginosa*, *Bacillus subtilis*, *Enterococcus faecalis, Escherichia coli,* herpes simplex and oral pathogens.
	Garlic	IV, AS, CT	Antibacterial, antifungal, antiviral and antiparasitic. Inhibits *Salmonella typhi, Vibrio cholerae, Tricophyton violaceum, Trichomonas vaginalis*, *Helicobacter pylori* and herpes simplex.
	Gentian	IV	Inhibited *Helicobacter pylori*.
	Ginger	IV, AS	Antibacterial, antiviral and antifungal.
	Goldenrod	IV	Antibacterial activity against species of *Bacillus, Proteus* and *Staphylococcus*.
	Goldenseal	IV	Demonstrated for the whole extract and berberine constituent against *Staphylococcus aureus*, *Streptococcus sanguis*, *E. coli*, *Pseudomonas aeruginosa.* Methanolic extract of rhizome inhibited *H. pylori* in vitro. Also demonstrated for berberine, activity against *Shigella dysenteriae*, *Bacillus subtilis*.
	Grapeseed extract	IV	Antibacterial and antifungal action.
	Green tea	IV, AS	Active against certain strains of *Staphylococcus* spp, *Streptococcus* spp, *Escherichia coli*, *Salmonella* spp; also *Corynebacterium suis*, *Helicobacter pylori*, *Porphyromonas gingivalis* and *Prevotella* spp, *Streptococcus mutans, S. salicarius and Helicobacter pylori*. Green tea is more active than black.
	Guarana	IV	Active against *Escherichia coli*, *Salmonella typhimurium*, *Staphylococcus aureus* and *Streptococcus mutans*.
	Gymnema sylvestre	IV	Active against *Bacillus pumilus*, *B. subtilis*, *Pseudomonas aeruginosa*, *Staphylococcus aureus, Klebsiella pneumoniae, P. aeruginosa, Escherichia coli* and *Salmonella typhi*.
	Hawthorn	IV	Antibacterial activity against Gram-positive *Micrococcus flavus, Bacillus subtilis* and *Lysteria monocytogenes*.

Major actions (known or suspected)	Herb/Nutrient	Evidence	Comments
	Honey	IV, CT	Leptospermum (manuka) honey can inhibit the growth of several important bacterial pathogens, including *Escherichia coli*, *Salmonella typhimurium*, *Shigella sonnei*, *Listeria monocytogenes*, *Staphylococcus aureus*, *Bacillus cereus* and *Streptococcus mutans*. Also useful against certain strains of methicillin-resistant *Staphylococcus aureus* and vancomycin-sensitive and resistant enterococci. Topical use.
	Hops	IV	Activity against the Gram-positive bacteria *Bacillus subtilis* and *Staphylococcus aureus* A, but almost no activity against the Gram-negative bacterium *Escherichia coli*.
	Horseradish	IV	Gram-negative and Gram-positive bacteria.
	Lavender oil	IV	Antibacterial, antifungal and mitocidal. Activity against *Staphylococcus aureus* and vancomycin-resistant enterococcus.
	Lemon balm	IV	Eugenol has antibacterial activity against *Escherichia coli* and *Staphylococcus aureus*.
	Licorice	IV, AS	Against Gram-positive and Gram-negative bacteria.
	Meadowsweet	IV	Bacteriostatic activity has been reported against *Staphylococcus aureus*, *S. epidermidis*, *Escherichia coli*, *Proteus vulgaris* and *Pseudomonas aeruginosa*.
	Mullein	IV	Antiviral and antibacterial.
	Myrrh	IV, CT	Activity against *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*.
	Noni	IV	Activity against *Escherichia coli, Mycobacterium tuberculosis* and *Ascaris lumbricoides*.
	Olive	IV	Activity against viruses, bacteria, yeasts and fungi. Activity against 8 strains of *H. pylori*.
	Orange	IV	Tuberculosis; against *Escherichia coli* and *Staphylococcus aureus*.
	Pelargonium	IV	Activity against *Staphylococcus aureus*, *Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalais, Micobacterium tuberculosis.*
	Peppermint	IV	Peppermint oil is active against *Helicobacter pylori*, *Staphylococcus aureus*, *Escherichia coli*, *Salmonella enteritidis*, *Listeria monocytogenes*, *Shigella sonnei* and *Micrococcus flavus,* and a variety of fungi.
	Perilla	IV	Activity against oral streptococci and *Porphyromonas gingivalis*.
	Prebiotics	AS	Through stimulation of beneficial bacteria growth, subsequent excretion of antimicrobial compounds inhibiting colonisation of pathogenic bacteria.
	Probiotics	IV	Specific strains of probiotics inhibit or kill *Helicobacter pylori*.
	Rhodiola	IV	Against *Staphylococcus aureus*.
	Rosemary	IV	Activity against a variety of bacteria and fungi.
	Sage	IV	Active against *Staphylococcus aureus*, *Escherichia coli*, *Salmonella* spp, *Shigella sonnei*, *Klebsiella ozanae*, *Bacillus subtilis* and various fungi, including *Candida albicans*. Antimicrobial activity also reported for sage oil.
	St John's wort	IV	Active against MRSA and other Gram-positive bacteria.

Continued

Major actions (known or suspected)	Herb/Nutrient	Evidence	Comments
	Shark cartilage	IV	Activity against protozoa, fungi and both Gram-positive and Gram-negative bacteria.
	Shatavari	IV	Activity against *Escherichia coli*, *Shigella sonnei*, *S. dysenteriae, S. flexneri, Vibrio cholerae, Salmonella typhi, Bacillus subtilis* and *Staphylococcus aureus*.
	Tea tree oil	IV, CT	Activity against *Corynebacterium* spp, *Klebsiella pneumoniae*, *Micrococcus luteus*, *Micrococcus varians*, *Micrococcus* spp, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Serratia marcescens*, *Staphylococcus aureus*, *S. capitis*, *S. epidermidis*, *S. haemolyticus*, *S. hominis*, *S. saprophyticus*, *S. warneri*, and *S. xylosus*. Successful trials in acne, methicillin-resistant *Staphylococcus aureus.* Topical use.
	Thyme	IV	Activity against *Escherichia coli*, *Listeria monocytogenes*, *Streptococcus mutans* and *Salmonella enterica*, *Helicobacter pylori, Klebsiella pneumoniae, Haemophilus influenzae* and *Candida albicans*.
	Tribulus	IV	Gram-negative and Gram-positive bacteria.
	Withania	IV, AS	Activity against *Staphylococcus aureus*, *Listeria monocytogenes*, *Bacillus anthracis*, *B. subtilis*, *Salmonella enteridis S. typhimurium* and *Escherichia coli*.
Antifungal			
	Baical skullcap	IV	Antifungal activity against *Candida albicans, Cryptococcus neoformans* and *Pityrosporum ovale.*
	Calendula	IV	Activity against *Aspergillus niger*, *Rhizopus japonicum*, *Candida albicans*, *Candida tropicalis* and *Rhodotorula glutinis*.
	Cinnamon	IV	
	Chitosan	AS	
	Clove oil	IV	Observed activity against species belonging to *Eurotium, Aspergilis* and *Penicillium* genera in vitro.
	Echinacea	IV	Activity observed against *Saccharomyces cerevisiae*, *Candida shehata*, *C. kefyr*, *C. albicans*, *C. steatulytica* and *C. tropicalis*.
	Ginger	IV	Ginger oils have shown activity against yeasts and filamentous fungi in vitro.
	Globe artichoke	IV	Antifungal activity.
	Goldenrod	IV	Inhibitory effects on *Candida* and *Cryptococcus* spp have been demonstrated for triterpenoid glycosides.
	Goldenseal	PH	Berberine constituent inhibits *Candida* spp.
	Honey	IV	Activity against *Candida albicans, C. glabrata* and *C. dubliniensis*.
	Hops	IV	Activity against the fungus *Trichophyton mentagrophytes* var. *interdigitale*, but almost no activity against the yeast *Candida albicans*.
	Lavender oil	IV	Activity against *Aspergillus nidulans* and *Trichophyton megatrophyles*.
	Orange essential oil		Effective against resistant fungal skin infections.
	Peppermint	IV	Fungistatic and fungicidal activity against *Trichophyton* and *Candida albicans*.
	Myrrh	IV	Activity against *Candida albicans*.

Major actions (known or suspected)	Herb/Nutrient	Evidence	Comments
	Rosemary	IV	
	Sage	IV	
	Tea tree oil	IV, CT	*Candida*, toenail onychomycosis.
	Thyme	IV	*Saccharomyces cerevisiae* and *Candida albicans*.
	Tribulus	IV	Strongest activity found to be against *Candida albicans*.
	Turmeric	IV, AS	Antifungal and antiprotozoan activity.
	Withania	IV	*Withanolides coagulens*, *Allescheria boydii*, *Aspergillus niger*, *A. flavus, Curvularia lunata*, *Drechslera rostrata*, *Epidermophyton floccosum*, *Fusarium oxysporum, F. verticilloides, Microsporum canis*, *Nigrospora oryzae*, *Pleurotus ostreatus* and *Stachybotrys atra*.
Antiviral			
	Aloe vera	IV, CT	Virucidal against herpes simplex 1 and 2, vaccinia virus, parainfluenza virus and vesicular stomatitis virus.
	Andrographis	IV	Andrographolides antiviral activity against HSV1 in vitro.
	Baical skullcap	IV, AS	
	Bitter melon	IV	Against EBV, HSV 1 & 2, coxsackievirus B3 and polio viruses.
	Calendula	IV	Virucidal activity against influenza viruses and suppresses the growth of herpes simplex virus.
	Chamomile	IV	Inhibitory activity against HIV activation; inhibits herpes virus in vitro.
	Cranberry	IV	Non-specific antiviral.
	Echinacea	IV	Activity against herpes simplex virus.
	Elder	IV	Effective against 10 strains of influenza.
	Ginger	IV	Antirhinoviral activity.
	Ginseng — Siberian	IV	Inhibits the replication of RNA-type viruses such as human rhinovirus, respiratory syncytial virus and influenza A virus.
	Glucosamine	IV	Antiviral activity.
	Green tea	IV	Interferes with virus absorption; antiviral activity has been identified against HIV, herpes simplex 1, influenza A and B, rotavirus and enterovirus, Epstein-Barr virus.
	Gymnema sylvestre		Antiviral activity.
	Hawthorn	IV	Herpes simplex 1.
	Hops	IV	Herpes simplex 1 and 2, cytomegalovirus and anti-HIV activity.
	Horseradish	IV	Activity against transmission of avian influenza.
	Lemon balm	IV, AS, CT	Herpes simplex 1 and 2, HIV.
	Licorice	IV, AS	Activity against SARS-CV, HIV, influenza A, Ebola virus, herpes simplex virus 1, Epstein-Barr virus, hepatitis B and C, encephalitis, respiratory syncytial virus, arboviruses, vaccinia virus and vesicular stomatitis virus.
	L-Lysine	IV, CT	Clinical trials show inconsistent results against herpes simplex virus.
	Mullein	IV	Antiviral activity against several influenza A and B strains, HSV.

Continued

Major actions (known or suspected)	Herb/Nutrient	Evidence	Comments
	Olive	IV	Antiviral activity against HIV.
	Orange		Potent inhibitory activity on rotavirus infection.
	Peppermint	IV	Antiviral activity demonstrated against HSV-1 and -2.
	Quercetin	IV, AS	Dose-dependent reduction in the infectivity and intracellular replication of HSV-1, polio virus type 1, para influenza virus type 3 and respiratory syncytial virus.
	Rosemary	IV	Antiviral activity against HSV and HIV-1.
	St John's wort	IV, AS	Antiretroviral activity appears to be photo-activated.
	Sage	IV	
	Stinging nettle	IV	Activity against HIV-1, HIV-2, human cytomegalovirus, respiratory syncytial virus and influenza A.
	Tea tree oil	IV	Activity against herpes simplex 1 and 2.
	Thyme oil	IV	Demonstrates antiviral activity against HSV-1 and -2 and acyclovir-resistant strain of the virus.
Antimalarial			
	Andrographis	IV, AS	Demonstrated antimalarial effects. Four xanthones isolated from *A. paniculata* demonstrated antimalarial effects against *Plasmodium berghei*.
	Green tea	IV	Strongly inhibits growth of *Plasmodium falciparum*.
	Turmeric	IV	Inhibition of growth of cloroquine-resistant *Plasmodium falciparum*.
Antiparasitic			
	Goldenseal	PH	Berberine inhibits *Entamoeba histolytica*, *Giardia lamblia*, *Trichomonas vaginalis*.
	Myrrh	CT	Effective against schistosomiasis, fascioliasis.
	Peppermint	IV, AS	Against nematodes and antigiardial activity.
Antimigraine (i.e. reducing frequency and/or severity of attacks)			
	Coenzyme Q10	CT	Mechanism unknown — possibly via mitochondrial stabilisation.
	Feverfew	CT, AS	Reduced frequency and severity of migraine headaches. Reduces serotonin release from platelets; possibly other mechanisms.
	Magnesium	CT	Mechanism unknown; does exert effect upon serotonin receptors, NO synthesis and release and neurotransmitters.
	SAMe	CT	Reduced pain reported.
	Vitamin B_2 (riboflavin)	CT	Reduced frequency and duration of migraines with large doses.
Antioxidant			
	Adhatoda	IV	Induces glutathione S-transferase and DT-diaphorase in lungs and forestomach, and superoxide dismutase and catalase in kidneys.
	Andrographis	AS	Increases liver superoxide dismutase, glutathione peroxidase, glutathione reductase and catalase concentrations, thereby increasing endogenous antioxidant production by the liver.
	Astragalus	AS	Raises superoxide dismutase activity in the brain and liver.

Major actions (known or suspected)	Herb/Nutrient	Evidence	Comments
	Baical skullcap	IV, AS	Baicalin antioxidant effect based on scavenging superoxide radicals; baicalein xanthine oxidase inhibitor.
	Beta-carotene	CT	Quenches singlet oxygen, scavenges peroxyl radicals and inhibits lipid peroxidation.
	Bilberry	PH, AS	Contains anthocyanosides shown to exhibit superoxide radical scavenging and cytoprotective activity.
	Brahmi	IV, AS	Direct free-radical-scavenging activity and increases endogenous antioxidant systems.
	Calendula	IV	Reduces levels of superoxide and hydroxyl radicals, suggesting a free-radical-scavenging effect; reduces lipid peroxidation.
	L-Carnitine	IV	Inhibits lipid peroxidation; may have an effect on superoxide-anion-radical scavenging and hydrogen-peroxide scavenging.
	Celery	AS	
	Chamomile	IV	Inhibits lipid peroxidation.
	Chondroitin	AS	Increases antioxidant enzymes and enhances antioxidant activity.
	Chromium	AS, CT	
	Cinnamon	IV	
	Clove oil	PH, IV	Antioxidant research focuses on constituent eugenol.
	Cocoa	IV, AS, CT	Activities attributed to high phenolics and flavonoids; reduces lipid oxidation.
	Coenzyme Q10		Buffers free radicals produced during oxidative phosphorylation and inhibits the mitochondrial permeability pore.
	Colostrum	AS	Increases superoxidase dismutase and glutathione peroxidase, and reduces oxidative stress and NO overproduction.
	Cranberry	IV	Polyphenolic compounds exert substantial antioxidant capacity. The antioxidant activity of flavonol glycosides are comparable or superior to that of vitamin E; increases excretion of oxalic and uric acid.
	Creatine	AS	
	Dandelion	AS	
	Dunaliella salina	AS	
	Echinacea	IV	Activity attributed to numerous antioxidant constituents found in echinacea, such as vitamin C, beta-carotene, flavonoids, selenium and zinc.
	Elder	IV	Activity attributed to flavonoid constituents quercertin, isoquercertin and rutin.
	Fenugreek	IV	
	Garlic	PH, IV	Capable of directly scavenging free radicals, and indirect activity by enhancing endogenous antioxidant systems such as glutathione, superoxide dismutase, catalase and glutathione peroxidase.
	Gentian	IV	
	Ginger	AS	Significantly lowers free-radical levels and raises endogenous antioxidant levels; protects against lipid peroxidation; modulates prostaglandin synthesis.

Continued

Major actions (known or suspected)	Herb/Nutrient	Evidence	Comments
	Ginkgo biloba	IV, AS	The extract and several of its individual constituents (quercetin, kaempferol) have demonstrated significant antioxidant properties; used topically, increases the activity of superoxide dismutase within skin.
	Ginseng — Korean	IV, AS	Suppresses lipid peroxidation.
	Globe artichoke	IV, CT	Increases plasma total antioxidant capacity.
	Glutamine		Precursor to glutathione.
	Goji	AS, CT	Stimulates endogenous antioxidant mechanisms; increases superoxide dismutase, glutathione peroxidase and reduces lipid peroxidation.
	Grapeseed extract	IV, AS	Significantly greater effects than vitamins C and E and beta-carotene; procyanidins prevent vitamin E loss and regenerate alpha-tocopherol radicals back to their antioxidant form.
	Green tea	IV, AS, CT	Inhibits lipid peroxidation; scavenges hydroxyl and superoxide radicals.
	Hawthorn	IV, AS	Direct and indirect activities.
	Honey	IV	Attributed to flavonoid content.
	Horse chestnut	IV	Dose dependently inhibits enzymatic and non-enzymatic lipid peroxidation in vitro.
	Lavender	IV	
	Lemon balm		
	Licorice	IV, CT	Reduces lipid peroxidation.
	Lutein and zeaxanthin	IV, AS	Increased glutathione levels and decreased retinal apoptosis.
	Lycopene	IV	Particularly against singlet oxygen and free radicals.
	Meadowsweet	IV	
	Mullein	IV	
	Noni	IV, CT	Inhibits COX-1 and -2 in vitro.
	Oats	CT	Avenanthramides increase antioxidant capacity.
	Olive leaf and olive oil	IV, CT	Attributed to phenolic compounds.
	Orange	IV	Inhibits lipid peroxidation.
	Peppermint	IV	Antioxidant and free-radical-scavenging activity.
	Perilla	IV	Multiple constituents identified exhibit antioxidant capacity.
	Policosanol	IV	Reduces oxidation of LDL-cholesterol.
	Quercetin	CT	
	Raspberry		Attributed to high tannin content.
	Red clover	PH	Isoflavones display antioxidant activity.
	Rhodiola	AS, CT	Increases endogenous antioxidant production.
	Rosemary	IV, AS	Chiefly due to carnosol and carnosic acid.
	Sage	AS	Chiefly due to labiatic acid and carnosic acid.
	St Mary's thistle	IV, AS	Antioxidant and free-radical-scavenging activity.
	SAMe	IV	Exhibited direct antioxidant activity in vitro.

Major actions (known or suspected)	Herb/Nutrient	Evidence	Comments
	Schisandra	IV	Direct activity and increases glutathione levels.
	Selenium		Essential component of glutathione peroxidase and thioredoxin reductase.
	Shark cartilage	IV	
	Shatavari	PH, IV, AS	Inhibition of lipid peroxidation and increase in antioxidant enzyme systems.
	Slippery elm	IV	Free-radical-scavenging activity may relate to anti-inflammatory action.
	Soy	IV, CT	Demonstrated in vitro; however clinical results inconclusive.
	Stinging nettle	IV, AS	Shown to scavenge free radicals, hydrogen peroxide and superoxide anion radicals; also regulates glutathione reductase, glutathione peroxidase and superoxide dismutase in vivo.
	Taurine		
	Thyme	IV	Exhibits potent antioxidant effects.
	Turmeric	IV, AS	Multiple mechanisms of action.
	Tyrosine	IV	Free-radical, superoxide-anion-radical and hydrogen-peroxide scavenging.
	Vitamin A		Free-radical-scavenging properties.
	Vitamin B_2 (riboflavin)		By itself, but also as part of the enzyme glutathione reductase.
	Vitamin B_3	IV	
	Vitamin B_5	IV	Indirect antioxidant action.
	Vitamin B_6	IV	Displayed antioxidant action in vitro and in vivo.
	Vitamin C	IV	Scavenges free-radical oxygen species and non-radical reactive species.
	Vitamin E	IV, AS, CT	Considered to be the most important and potent lipid-soluble antioxidant. It prevents free radical damage to polyunsaturated fatty acids within the phospholipid layer of each cell membrane and oxidation of LDL-cholesterol.
	Wild yam	PH	
	Withania	IV, AS	Most likely by increasing activity of endogenous antioxidant enzymes.
	Zinc		Indirect and direct activities.
Antiparasitic — See listing under Antimicrobial			
Antiplatelet — See listing under Blood thinning			
Antipruritic			
	Chamomile	AS	
	Chickweed	TU	Topical use; effect due to saponins.
	Oats	CT	Topical use.
Antipyretic			
	Andrographis	IV, AS, CT	
	Fenugreek	AS	
	Willowbark	PH	Effect chiefly due to salicylate content.

Continued

Major actions (known or suspected)	Herb/Nutrient	Evidence	Comments
Antispasmodic			
	Adhatoda	AS	Essential oil.
	Brahmi	AS	Acts on smooth muscle; effect due to inhibition of calcium influx into the cell.
	Calendula	IV	Effect due to calcium-channel-blocking and cholinergic activity.
	Chamomile	IV	Dose dependent.
	Cinnamon	AS	Active constituent is cinnameldehyde.
	Clove oil	PH	Effect due to the eugenol, beta-caryophyllene component.
	Feverfew	IV	Decreases vascular smooth muscle spasm.
	Globe artichoke	IV	
	Goldenrod	AS	
	Hops	TU	
	Horseradish		
	Kava kava	IV, AS	Acts on skeletal muscles.
	Magnesium		
	Myrrh	EV	Due to T-cadinol, and several minor components.
	Peppermint	IV, CT	Multiple mechanisms identified.
	Rosemary	TU	Used for mild cramp-like gastrointestinal and biliary upsets, as well as for tension headache, renal colic and dysmenorrhoea.
	Sage	AS	
	St John's wort	AS	Most likely mediated via GABA activity.
	Saw palmetto	IV	
	Thyme	IV	
	Tribulus	IV, PH	Dose-dependent decrease in peristaltic movements.
	Turmeric	AS	Smooth muscle relaxant, possibly through calcium-channel blockade.
	Valerian	IV, AS	Acts on smooth muscle.
	Wild yam	TU	
Antithrombotic — See listing under Blood thinning			
Antitussive			
	Adhatoda	AS	Comparable to codeine when cough is due to irritant stimuli.
	Chickweed	TU	Saponins irritate mucous membranes.
	Cocoa	AS	Antitussive effect may be mediated peripherally through an inhibitory affect on afferent nerve activation.
	Eucalyptus	AS, CT	Various mechanisms.
	Licorice	AS	Mediated by liquiritin apioside.
	Passionflower	AS	
	Shatavari	AS	Dose-dependent cough inhibition.
	Thyme	AS	

Major actions (known or suspected)	Herb/Nutrient	Evidence	Comments
Anti-ulcer/anti-ulcerogenic (i.e. prevention and/or treatment)			
	Brahmi	AS	Fresh juice of whole plant enhanced mucin secretion and mucosal glycoprotein and decreased cell shedding.
	Chamomile	AS	Prevented formation of ulcers and reduced healing time.
	Fenugreek	IV, AS	Soluble gel fraction formed by polysaccharide and/or flavonoid components.
	Ginger	AS	
	Ginseng — Korean	AS	Mechanism attributed to inhibition of acid secretion, increased mucin secretion and antioxidant properties.
	Lemon balm	AS	Activity associated with reduced acid output and increased mucin secretion, an increase in prostaglandin E_2 release and a decrease in leukotrienes.
	Licorice	CT	Ability to promote mucosal repair and reduce symptoms of active ulcer.
	Meadowsweet	IV, AS	Protective effects against stomach ulcers induced by acetylsalicylic acid; however, no protection was seen against ulcers produced under high-acid environments or due to stimulation by histamine. Effect may be prostaglandin-mediated.
	St Mary's thistle	AS	Associated with reduced acid output, increased mucin secretion, increased prostaglandin E_2 release and decreased leukotriene release.
	Shatavari	AS	Inhibition of hydrochloric acid and protection of gastric mucosa.
	Turmeric	CT	May reduce symptoms.
Antiviral — See listing under Antimicrobial			
Anxiolytic — See listing under Anti-anxiety			
Astringent			
	Bilberry	PH	Attributed to significant tannic content.
Blood thinning			
Anticoagulant			
	Dong quai	CT	Ferulic acid found to inhibit platelet aggregation.
	Evening primrose oil	TH	PGE_1 production results in a cascade of reactions that ultimately inhibit platelet aggregation and cause vasodilation.
	Ginkgo biloba	CT	
	Meadowsweet	IV, AS	
	Ginseng — Siberian	CT, AS	Decreases blood coagulation normally induced by intensive training of athletes.
	Turmeric	IV, AS	Demonstrated for curcumin.
Antiplatelet			
	Andrographis	IV, AS, CT	Andrographolide, AP3 and four flavonoids inhibit thrombin and PAF-induced platelet aggregation. Andrographolide and AP3 inhibit extracellular signal-regulated kinase 1/2 pathway in vitro.
	Baical skullcap	IV	
	Clove oil	IV	Due to the eugenol component.

Continued

Major actions (known or suspected)	Herb/Nutrient	Evidence	Comments
	Cocoa	IV, CT	Due to polyphenol content.
	Dong quai	CT	Ferulic acid found to inhibit platelet aggregation.
	Evening primrose oil	TH	PGE_1 production results in a cascade of reactions that ultimately inhibit platelet aggregation and cause vasodilation.
	Feverfew	IV, AS, CT	No significant effects were seen in a clinical study of 10 patients receiving feverfew.
	Fish oils	AS, CT	Enhance anti-aggregatory and anti-adhesive platelet activity and reduce several coagulation factors.
	Flaxseed	PH	
	Garlic	IV, CT	Multiple mechanisms.
	Ginger	CT	Gingerols inhibit platelet activation.
	Ginkgo biloba	CT	Platelet-activating-factor antagonist.
	Ginseng — Korean	IV, AS	Ginsenosides inhibit platelet aggregation.
	Ginseng — Siberian	IV	3,4-dihydroxybenzoic acid constituent.
	Grapeseed extract	IV	Combination of grapeseed and grape skin produces a greater effect.
	Green tea		
	Guarana	IV, AS	Decreases thromboxane synthesis.
	Licorice	IV, AS	Isoliquiritigenin inhibits platelet aggregation in vitro and in vivo.
	Myrrh	CT	Gum guggul fraction.
	Policosanol	AS, CT	Inhibits platelet aggregation.
	Rosemary	IV, AS	
	Schisandra	IV	Several lignans inhibit platelet-activating factor.
	Turmeric	IV, AS	Demonstrated for curcumin.
	Vitamin E	IV	Demonstrated in vitro, but in vivo tests have been inconsistent; likely only at very high doses.
	Willowbark	CT	
Antithrombotic			
	Andrographis	AS, CT	Inhibits production of thromboxane A2 and stimulates PGE_2.
	Baical skullcap	IV	Baicalein inhibited the elevation of calcium induced by thrombin and thrombin receptor agonist peptide.
	Evening primrose oil	TH	PGE_1 production results in a cascade of reactions that ultimately inhibit platelet aggregation and cause vasodilation.
	Fish oils	AS, CT	Inhibits thromboxane A2 and coagulation factors.
	Flaxseed	PH	Inhibition of AA, resulting in EPA replacing it on cell membrane, decreases thromboxane synthesis.
	Garlic	IV, CT	Inhibits thromboxane A2 formation.
	Ginseng — Siberian	AS	Protects against immobilisation-induced thrombosis.
	Guarana	IV, AS	Decreases thromboxane synthesis.
	Licorice	IV, AS	Effective thrombin inhibitor in vivo.
	Policosanol	CT	Inhibits thromboxane.

Major actions (known or suspected)	Herb/Nutrient	Evidence	Comments
	Rosemary	IV, AS	Demonstrated in vitro and in vivo.
Bone density protection			
	Calcium	CT	Assists with calcium deficiency, BMD and osteoporosis prophylaxis.
	Chromium	CT	Modulative of insulin, reduced bone resorption and promotion of collagen by osteoblasts.
	Evening primrose oil	AS	Increases intestinal calcium absorption and balance.
	Hops	CT	Exerts oestrogen-like activities on bone metabolism.
	Licorice	IV	Constituent glabridin may enhance osteoblast function.
	L-Lysine	CT	Increases intestinal calcium absorption.
	Magnesium	CT	
	Quercetin	IV, AS	Prevents bone loss by affecting osteoclastogenesis.
	Red clover	PH, AS, CT	
	Red yeast rice	IV, CT	Strong bone anabolic effects in vitro and in vivo attributed to naturally occurring flavonoids and statins.
	Schisandra	PH	Lignans stimulated proliferation and activity of alkaline phosphatase in osteoblasts.
	Soy	IV, CT	Stimulates the synthesis and expression of alkaline phosphatase in osteoblasts. May be more effective in perimenopausal subjects.
	Vitamin C	EP, CT	
	Vitamin D	CT	Mediated through maintaining calcium and phosphorus homeostasis and osteocalcin expression, PTH; oestrogen biosynthesis and cell growth regulation.
Capillary stabilisation			
	Bilberry	AS	Stabilises membrane phospholipids; increases the synthesis of mucopolysaccharides of the connective ground substance and restores altered mucopolysaccharidic pericapillary sheath; improves ischaemic damage and preserves capillary perfusion; inhibits increased permeability of reperfusion and saves arteriolar tone.
	Ginkgo biloba	AS	Due to proanthocyanidin content.
	Grapeseed extract	AS, CT	Cross-links collagen fibres, reducing capillary permeability.
	Hawthorn		Flavonoid content improves vascular repair.
	Horse chestnut	IV, AS	Multiple mechanisms.
	Vitamin C		Essential for the formation of collagen.
Cardioprotective			
	Arginine		Formation of NO.
	Beta-carotene	AS	Antioxidant mechanisms.
	Cocoa	EP	Polyphenol content responsible for protective effects.
	Coenzyme Q10	AS, CT	Various mechanisms, including antioxidant activity.
	Dong quai	IV, AS	Prolonging of cardiac refractory period and correcting atrial fibrillation.
	Fish oils	CT	Various mechanisms.
	Flaxseed oil	CT	Various mechanisms associated with ALA.

Continued

Major actions (known or suspected)	Herb/Nutrient	Evidence	Comments
	Folate		Reducing Hcy.
	Ginkgo biloba	CT	Promotes vasodilation and increased blood flow through arteries, veins and capillaries.
	Ginseng — Korean	IV, AS	Diverse mechanisms including antioxidant, vasomotor functioning, reduced platelet adhesion, ion channels and altered neurotransmitter release.
	Ginseng — Siberian	AS	Activity due to increased endogenous opioid peptide levels.
	Grapeseed extract	IV, AS	Various mechanisms.
	Glutamine	IV	Maintains myocardial glutamate, ATP and phosphocreatine and prevents lactate accumulation in vitro.
	Hawthorn	AS, CT	Multiple mechanisms demonstrated in vitro and in vivo.
	Lycopene	EP	
	Magnesium	AS, CT	Multiple mechanisms.
	Olive	CT	Multifaceted: reduced lipidoxidation, reduced LDL oxidation; reduces oxidative damage, inflammation, blood pressure; anti-atherogenic and anti-thrombotic.
	Quercetin	IV, AS	Vasorelaxant, anti-inflammatory and antioxidant.
	Rhodiola	AS	
	St Mary's thistle	IV	Partly due to antioxidant effects.
	Schisandra	AS	Activity seen for schisandrin B constituent.
	Selenium	CT	
	Shatavari	AS	
	Soy	ES, CT	Decreased LDL and triglycerides and increased HDL.
	Tribulus	AS, CT	Possible due to inhibition of ACE activity.
	Vitamin C	EP	
	Vitamin E	IV, CT	Regulates vascular smooth muscle cell proliferation; anti-inflammatory, antioxidant and antiplatelet.
	Withania	PH, IV, AS	Most likely due to restoration of myocardial oxidant-antioxidant balance and marked anti-apoptotic properties.
Chemoprotection — See listing under Anticancer			
Choleretic (i.e. increased bile production and flow)			
	Andrographis	AS	Dose-dependent increase in bile flow and bile salt and acid production.
	Chamomile	AS	Chamomile increases bile production.
	Dandelion (root)	TU	
	Devil's claw	TU	Increased bile production.
	Ginger	AS	
	Globe artichoke	AS, CT	Increased bile secretion.
	Peppermint	AS, CT	Exerts relaxing effect on gall bladder and small intestine.
	St Mary's thistle	AS	Impact on bile secretion.
Chologogue (i.e. increased bile flow)			
	Celery	AS	Increases bile acid secretion.
	Globe artichoke	AS	Increased bile flow.

Major actions (known or suspected)	Herb/Nutrient	Evidence	Comments
	Turmeric	IV, AS	Stimulates contraction of the gall bladder and promotes the flow of bile.
	Wild yam	AS	
Chondroprotective			
	Chondroitin	IV, AS, CT	Various mechanisms.
	Devil's claw	IV, AS	The tissue inhibitor of metalloproteinase-2 is involved.
	Glucosamine	IV, CT	Proteoglycan biosynthesis and production of hyaluronic acid; increases APL activity, collagen synthesis, osteocalcin secretion and mineralisation in osteoblastic cells.
	SAMe	IV, AS	
	Vitamin B_3	CT	Via suppression of cytokine-mediated induction of NO synthase.
	Withania	IV, AS	
CNS sedative			
	Chamomile	AS, CT	Demonstrating a benzodiazepine-like activity.
	Hops	TU, CT, AS	Through activation of melatonin receptors.
	Lavender oil	AS, CT	Inconsistent results.
	Lemon balm	CT	High doses.
	Kava kava	IV, AS	
	Passionflower	AS	Mechanism unknown.
	Peppermint	AS	
	Valerian	IV, AS, CT	
CNS stimulant			
	Guarana	CT	Possibly due to caffeine content.
	Peppermint	AS	Possibly due to menthone, mediated by dopamine.
Cognitive enhancement/activator			
	Albizia	AS	Effects due to saponins.
	Astragalus	AS	In combination with other herbs.
	Brahmi	AS, CT	Possible mechanisms of action are antioxidant and anticholinesterase activity.
	Ginkgo biloba	IV, AS, CT	Cholinergic activity.
	Ginseng — Korean	CT	Enhances survival of newly formed neurons.
	Guarana	AS, CT	
	Lemon balm	CT	Dose dependent, cholinergic.
	Licorice	AS	May be due to cholinergic effects.
	Quercetin	AS	
	Rhodiola	AS, CT	Promotes release of monoamine neurotransmitters.
	Rosemary	CT	
	St John's wort	CT	Cholinergic effects.
	Soy	PH, CT	May mimic the action and functions of oestrogen in the brain.
	Tyrosine	CT	
	Vitamin B_6		Possibly due to reduction of homocysteine.

Continued

Major actions (known or suspected)	Herb/Nutrient	Evidence	Comments
	Withania	IV, AS	Potent acetylcholinesterase inhibitory activity exhibited in vitro.
Diuretic			
	Celery	TU	
	Dandelion (leaf)	TU	Considered a potassium-sparing diuretic.
	Elder	TU, IV	Study found elder exhibited diuretic properties comparable to hydrochlorothiazide.
	Globe artichoke	AS	
	Goldenrod	AS	Excretion of calcium can increase whereas excretion of potassium and sodium decreases.
	Green tea	PH	Chiefly due to caffeine content.
	Guarana	PH	Chiefly due to caffeine content.
	Horseradish	TU	
	Stinging nettle leaf	AS	
	Tribulus	AS	With high doses.
Expectorant			
	Chickweed	TU	Saponins irritate mucous membranes.
	Licorice	TU, TH	Stimulates tracheal mucus secretion, facilitating elimination of mucus from the respiratory tract.
	Mullein	PH	Due to saponins.
	Thyme	AS	Due to saponins.
Ergogenic effects			
	Rhodiola	AS, CT	Results conflicting.
Gastrointestinal effects			
	Astragalus	AS	Improves gastrointestinal motility; strengthens the movement and muscle tone of the small intestine.
	Bilberry	IV	Specific anthocyanin-increased efficiency of gastric mucosal barrier.
	Cinnamon	AS	
	Colostrum	IV, AS, CT	Improves gut permeability and reduces NSAID-induced damage.
	Dong quai	AS	Through promotion of growth factors, antioxidant activity and anti-inflammatory effects.
	Fenugreek	AS	Enhances pancreatic lipase activity, intestinal lipase activity and the disaccharides sucrase and maltase.
	Gentian	TU, CT	Stimulates the flow of saliva, gastric juice and bile secretion.
	Ginger	AS, CT	Stimulates the flow of saliva, bile and gastric secretions; anti-ulcer activity.
	Ginseng — Korean	IV	Carminative action.
	Glucosamine	PH	Glycoproteins protect bowel mucosa.
	Glutamine	IV, AS	Aids in the proliferation and repair of intestinal cells.
	Guarana	CT	Increases gastric acid secretion and delays gastric emptying time in combination with yerbe mate and damiana.
	Hawthorn		Dose-dependent gastroprotective activity.

Major actions (known or suspected)	Herb/Nutrient	Evidence	Comments
	Horseradish		Oil may exert a gastric irritant effect.
	Lavender	TU	Carminative action.
	Licorice	AS	Increases mucosal blood flow and mucus production.
	Meadowsweet	IV	Involves PG-mediated mechanisms.
	Orange essential oil	TU	Carminative action and antispasmodic.
	Peppermint	CT	Relaxation of GIT sphincters.
	Prebiotics	AS	Through stimulation of beneficial bacteria growth, subsequent excretion of antimicrobial compounds inhibiting colonisation of pathogenic bacteria.
	Probiotics	IV, AS, CT	Promotes health-digestive function; eradicates GIT infections and management of GIT disease states.
	Psyllium	CT	Bulking agent, antidiarrhoeal; prevents constipation.
	St John's wort	PH, AS	Inhibits gastric motility.
	St Mary's thistle	AS	Dose dependent.
	Shatavari	IV, AS	Antiemetic, antiulcerogenic, antidiarrhoeal.
	Slippery elm	TU	Demulcent effects.
	Taurine		Conjugation of bile acids.
	Turmeric	IV, AS	Hepatoprotective, cholagogue, hypolipaemic, antispasmodic, wound healing and anti-inflammatory.
	Lavender	TU	Carminative action.
Hepatoprotective			
	Andrographis	AS	Increases liver superoxide dismutase, glutathione peroxidase, glutathione reductase and catalase concentrations, thereby increasing endogenous antioxidant production by the liver; hepatoprotective effect of andrographolide is more potent than that of silymarin.
	Astragalus	AS	Increases liver glutathione levels.
	Baical skullcap	AS	Baicalein, baicalin and wogonin shown to inhibit oxidation and nitration; action may be due to increased metatonin levels; perhaps glutathione sparing mechanism.
	Brahmi	AS	
	Calendula	IV, AS	
	Clove oil	AS	
	Dong quai	AS	Found to exert antioxidant, antiproliferative and pro-apoptotic activities in hepatic stellate cells in vitro.
	Dunaliella salina	AS, CT	May be due to isomeric forms of carotene and other oxygenated carotenoids.
	Fenugreek	IV	
	Garlic	IV, AS	Glutathione-sparing effect on liver.
	Ginger	AS	Effect mediated by antioxidative mechanism.
	Ginseng — Korean	AS	
	Ginseng — Siberian	AS	Protective effect due to water-soluble polysaccharides.
	Globe artichoke	AS	Increases hepatic regeneration, blood flow and antioxidant capacity.
	Grapeseed extract	IV, AS	Inhibits lipid peroxidation and antioxidant activity.

Continued

Major actions (known or suspected)	Herb/Nutrient	Evidence	Comments
	Hawthorn	AS	May be mediated through antioxidant mechanisms.
	Lemon balm	AS	Mediated through antioxidant mechanisms.
	Licorice	IV, AS, CT	Decreases hepatocellular damage in chronic hepatitis B and C; modulates inflammatory mediators and enhances antioxidant mechanisms.
	Meadowsweet	IV, AS	Improved liver function.
	Perilla	AS	Possibly due to antioxidant mechanisms.
	Quercetin	IV, AS	Possibly due to antioxidant mechanisms.
	Rosemary	AS	Attributed to antioxidant mechanisms and enhancing glutathione S-transferase.
	Rhodiola	AS	
	St Mary's thistle	IV, AS, CT	Protective against carbon tetrachloride-induced liver cirrhosis, paracetamol-induced liver peroxidation, and side effects of cyclosporin, phenothiazine, butyrophenone, erythromycin, amitriptyline and nortriptyline, oestradiol, amanita phalloides, tacrine and iron overload.
	SAMe	CT	Significantly increases hepatic glutathione levels.
	Schisandra	IV, AS, CT	Schisandrin B potentiates efficiency of hepatic glutathione antioxidant system, inhibits lipid peroxidation; gomisin A found to inhibit the appearance of histological changes such as degeneration and necrosis of hepatocytes.
	Shatavari	IV	Significantly reduces hepatic enzymes in vitro.
	Stinging nettle	AS	Maintains antioxidant enzyme activity.
	Turmeric	IV, AS	Potent antioxidant; appears to chelate hepatic serum iron in vivo.
	Vitamin B_{12}	AS	
	Withania	AS	Inhibits phase I and activates phase II detoxification enzymes.
Hepatorestorative (i.e. liver repair)			
	Ginseng — Korean	AS	
	St Mary's thistle	AS, CT	Various mechanisms.
	Schisandra	AS	Gomisin A increases ornithine decarboxylase activity, which is important during the early stages of regeneration, and suppresses fibrosis proliferation.
Homocysteine level reduction			
	Folate	CT	
	Garlic	CT	May be through inhibition of CD36 expression and OxLDL uptake by macrophages.
	Vitamin B_6	CT	With B_{12} and folate.
	Vitamin B_{12}	CT	With B_6 and folic acid.
Hypertensive			
	Guarana	PH	Effects due to caffeine content.
Hypoglycaemic/improving blood-sugar control			
	Aloe vera	CT	One clinical study found that blood-sugar levels reduce steadily in people treated with aloe gel, compared with a control group.

Major actions (known or suspected)	Herb/Nutrient	Evidence	Comments
	Andrographis	IV, AS	Exerts a strong dose-dependent action on insulin production; inhibition of alpha-glucosidase; lowers plasma glucose by enhancing glucose utilisation and may alter glucose absorption.
	Baical skullcap	AS	Mechanisms of action include 5-alpha-aldose inhibition and alpha-glucosidase inhibition.
	Bilberry	AS	Bilberry extracts contain myrtillin, which has been shown to possess hypoglycaemic actions.
	Bitter melon	CT, AS	Hypoglycaemic activity attributed to steroidal saponins, insulin-like peptides and alkaloids. Increases renewal of beta-cells and stimulates insulin secretion.
	Calendula	AS	
	L-Carnitine	CT	Improves insulin secretion, peripheral glucose use and tissue insulin sensitivity.
	Chromium	CT	Blood-glucose regulation; multiple mechanisms.
	Cocoa	CT	
	Cinnamon	CT	
	Cloves	IV	Phenolic compounds may be key constituent responsible.
	Damiana	AS	Experimental model found significant reduction of hyperglycaemic peak, exerting hypoglycaemic effect comparable to tolbutamide.
	Devil's claw	AS	Dose dependent.
	Elder	IV	Increased insulin secretion, muscle glucose uptake, glucose oxidation and glycogenesis in pancreatic beta cells
	Evening primrose oil	AS	
	Fenugreek	AS, CT	Delays glucose absorption and enhances its utilisation; increases tissue insulin sensitivity.
	Garlic	AS, CT	Produces changes in glucose tolerance and insulin secretion.
	Ginger	IV, AS	Hypoglycaemic activity indicated, improves insulin sensitivity.
	Ginseng — Korean	IV, AS, CT	May inhibit glycated haemoglobin.
	Ginseng — Siberian	AS, CT	Increased insulin release, insulin sensitivity and enhanced glucose utilisation.
	Globe artichoke	AS	
	Goji	AS	Polysaccharides and vitamin oxidants responsible for effects.
	Gymnema sylvestre	IV, AS, CT	Multiple mechanisms involved, including reduced intestinal glucose absorption, inhibition of glucose transport and suppression of glucose-mediated release of GIP.
	Hawthorn	AS	
	Myrrh	AS	Increased glucose tolerance.
	Oats	CT	Reduces postprandial glycaemic response.
	Olive leaf	AS	Potentiation of glucose-induced insulin release and increased peripheral uptake of glucose.
	Psyllium	AS, CT	Modulates glycaemic response through various mechanisms.
	Quercetin	AS	Reduction of blood glucose

Continued

Major actions (known or suspected)	Herb/Nutrient	Evidence	Comments
	Red yeast rice	AS	Acetylcholine release, generating subsequent stimulation of muscarinic M3 receptors in pancreatic cells that effect insulin release.
	Rhodiola	IV, AS	Multiple mechanisms.
	Sage	AS	Decreases serum glucose without affecting insulin release.
	St Mary's thistle	IV	Multiple mechanisms.
	Stinging nettle	AS	Decreases glucose absorption and modifies blood glucose levels.
	Taurine	AS	
	Vitamin B_3	CT	Impairs glucose control in high doses; protects beta cells of the pancreas after onset of type 1 diabetes.
	Vitamin B_6	AS	Reduced diabetic complications.
	Vitamin D	IV, AS	Essential for insulin activation and secretion.
	Withania	IV, AS	Reduced blood glucose and insulin; improved glucose tolerance and insulin sensitivity.
	Zinc		May be mediated via direct and indirect antioxidant role.
Hypotensive — See listing under Antihypertensive			
Immunomodulating			
	Aloe vera	IV, AS	Immune stimulant: antiviral, antitumour and non-specific immunostimulant activity; protective against a variety of fungi and bacteria.
	Andrographis	IV, AS, CT	Immune stimulant: antigen-specific and non-specific immune responses in vivo; immunostimulant activity of the whole extract is greater than the isolated andrographolide constituent. Immunodepressant: andrographolide found to decrease IFN-gamma and IL-2 production; may interfere with T-cell proliferation, cytokine release and maturation of dendritic cells; additionally inhibits T-cell antibody response.
	Arginine		Triggers the release of growth-hormone-stimulating cytotoxic activity of macrophages, natural killer cells, cytotoxic T-cells and neutrophils.
	Astragalus	IV, AS, CT	Immune stimulant: stimulates macrophage activity and enhances antibody responses.
	Baical skullcap	IV, AS, CT	Immune stimulant.
	Beta-carotene	CT	Multiple mechanisms involved.
	Calendula	IV	Stimulates phagocytosis of human granulocytes.
	Chamomile	IV	Immune stimulant.
	Chromium	IV	Chromium has both immunostimulatory and immunosuppressive effects, as shown by its effects on T- and B-lymphocytes, macrophages and cytokine production.
	Colostrum	AS	Immune modulation.
	Dong quai	IV, AS	Enhanced cell-mediated immunity; upregulation of IL-2 and IFN-gamma; suppression of humoral immunity.
	Echinacea	CT	Immune stimulant: activation of polymorphonuclear leucocytes and NK cells and increased T-cells; inhibited NFkappaB, TNF-alpha, NO and cytokines.
	Elder	IV	Increased production of inflammatory cytokines.

Major actions (known or suspected)	Herb/Nutrient	Evidence	Comments
	Fenugreek	AS	Immune stimulant: enhanced humoral immunity, significant increases in macrophage activity and a stimulatory effect on lymphoproliferation.
	Fish oils		
	Garlic	CT	Immune stimulant.
	Ginger	IV, AS	In vitro and in vivo research suggests that ginger extract exerts some degree of immunomodulatory activity.
	Ginkgo biloba	AS	Immune stimulant attributed to antioxidant properties.
	Ginseng — Korean	IV, AS, CT	Based on the production of cytokines, activation of macrophages, stimulation of bone marrow cells and stimulation of inducible NO synthesis.
	Ginseng — Siberian	IV, AS, CT	Stimulates general non-specific resistance and influences T-lymphocytes, natural killer cells and cytokines.
	Glutamine	AS, CT	Multiple mechanisms.
	Goji	IV	Action includes activation of T cells, B cells and NK cells.
	Goldenseal	IV	
	Honey	AS	Increased humoral immunity in immunocomputent mice.
	Iron	IV, CT	Vital for cell proliferation.
	Licorice	AS	
	Lutein	AS, CT	Modulates cellular and humoral-mediated immune responses.
	Perilla	IV	Stimulates phagocytosis.
	Prebiotics	IV, AS	Through stimulation of beneficial bacteria growth subsequent excretion of antimicrobial compounds inhibiting colonisation of pathogenic bacteria; promoting the production of SCFAs.
	Probiotics	IV, AS, CT	Probiotics bind to intestinal epithelial cells and inhibit the binding of pathogenic bacteria to the gut wall by producing inhibitory substances such as bacteriocins, lactic acid and toxic oxygen metabolites.
	Quercetin	IV, AS	Induction and inhibition of TH1 cytokines.
	Rhodiola	CT	
	Sage	PH, IV	
	Selenium	AS, CT	Confirmed in both animal studies and human trials, immune modulation is in part due to improved activation and proliferation of B-lymphocytes and enhanced T-cell function. Selenium concentrations significantly decrease during stages of acute infection, suggesting either increased utilisation and/or excretion or decreased absorption during this period.
	Shark cartilage	IV	Immune stimulant found to induce TH1 inflammatory cytokines and appears to inhibit TH2 cells.
	Shatavari	IV, AS	Various mechanisms.
	Turmeric	IV, AS	Curcumin has demonstrated both immunostimulant and immunosuppressant activity.
	Vitamin A	AS	Immune-stimulant role includes expression of mucins and keratins, lymphopoiesis, production of antibodies, and the function of neutrophils, natural killer cells, macrophages and T- and B-lymphocytes. Potentiates antibody responses and lymphocyte proliferation in response to antigens. Restores the integrity and function of mucosal surfaces.

Continued

Major actions (known or suspected)	Herb/Nutrient	Evidence	Comments
	Vitamin B_6	CT	Increased T-helper and T-lymphocyte cells in critically ill patients.
	Vitamin B_{12}		Acts as an immunomodulator for cellular immunity.
	Vitamin C	IV, CT	Immune stimulant: favourably modulates lymphocytes and phagocytes, regulates natural killer cells and can influence antibody and cytokine synthesis in certain situations.
	Vitamin D	IV, AS	Promotes differentiation of macrophages and influences cytokine production.
	Vitamin E	CT	Regulates immunocompetence: increases humoral antibody production, resistance to bacterial infections, cell-mediated immunity, the T-lymphocyte response, tumour necrosis factor production and natural killer cell activity.
	Withania	AS	Immunomodulating effects include an increase in white blood cell, platelet and neutrophil counts, increases in interferon-gamma and interleukin-2 levels, and a reduction in tumour necrosis factor level.
	Zinc	AS, CT	Essential for normal development and function of cells mediating non-specific immunity, such as neutrophils and natural killer cells, and affects development of acquired immunity and T-lymphocyte function.
Laxative			
	Aloe vera	AS	Anthraquinones increase intestinal water content, stimulate mucus secretion and induce intestinal peristalsis.
	Dandelion (root)	TU	Mild activity.
	Magnesium	PH	In high doses.
	Oats		Acts as a bulking laxative.
Lipid-lowering			
	Astragalus	CT	In combination with other herbs.
	Baical skullcap	AS	Flavonoid component; mechanism may be due to increased expression of lecithin cholesterol acyltransferase.
	Bilberry	AS	Decreases plasma triglyceride levels.
	Bitter melon	AS	Decreases triglyceride and LDL levels and increases HDL.
	Calcium	CT	Reduced LDL-cholesterol levels by 4.4%, increased HDL-cholesterol levels 4.1% in one study.
	Calendula	AS	
	L-Carnitine	CT	Reduces serum lipoprotein-a levels; changes in other lipid parameters inconsistent.
	Celery	AS	Reduces total serum cholesterol levels.
	Chitosan	CT	Forms complexes with various fats including cholesterol.
	Chromium	CT	Decreases triglyceride levels, total and LDL cholesterol and increases HDL.
	Cinnamon	AS	
	Cocoa	CT	Attributed to cocoa polyphenols and chocolate fatty acids.
	Evening primrose oil	AS	Demonstrated lipid-lowering effects.
	Fenugreek	AS, CT	May be attributed to interaction of fibre and steroidal saponins with bile salts in digestive tract.

Major actions (known or suspected)	Herb/Nutrient	Evidence	Comments
	Fish oils	CT	Decreases triglyceride levels.
	Flaxseed oil	CT	
	Flaxseeds	CT	
	Garlic	IV, CT	Demonstrated elevation in HDL and reduction in triglyceride levels; mechanisms attributed to inhibition of monoxygenases and HMG-CoA reductase.
	Ginger	CT, AS, EP	May reduce cholesterol and triglyceride levels and development of atherosclerotic lesions.
	Ginseng — Korean	AS, CT	Reduces total cholesterol, triglyceride, LDL and increases HDL.
	Globe artichoke	CT	Reduction in total cholesterol through indirect modulation of hydroxymethylglutaryl CoA reductase activity.
	Goji	AS	Reduces plasma triglyceride and cholesterol levels.
	Goldenseal	CT	Demonstrated for berberine constituent.
	Grapeseed extract	AS, CT	LDL- and triglyceride-lowering activities.
	Green tea	IV	
	Gymnema sylvestre	AS, CT	Serum-cholesterol- and triglyceride-lowering activities.
	Hawthorn	AS, CT	
	Licorice	AS	Reduces total lipids, cholesterol, triglycerides, LDL, VLDL and increases HDL.
	Lycopene	IV, CT	Reduces LDL-cholesterol level.
	Magnesium	CT	Increases molar ratio of apolipoprotein A1:apolipoprotein B; reduces triglyceride levels.
	Myrrh	CT, AS	Guggul or certain constituents within *Commiphora mukul* reduce triglyceride and cholesterol levels.
	Oats	CT	Beta-glucans increase bile acid synthesis and decrease serum cholesterol.
	Olive	CT	Reports inconsistent.
	Perilla	IV, AS	Suppression of HMG-CoA and stimulating acyl-CoA-oxidase.
	Policosanol	AS, CT	Conflicting outcomes. Lowers total cholesterol levels, increases HDL and reduces LDL levels.
	Probiotics	CT	Particular strains may enzymatically deconjugate bile acids and alter the utilisation of cholesterol.
	Psyllium	CT	Alters cholesterol metabolism, increases hepatic cholesterol catabolism and increases faecal bile acid excretion.
	Red clover	CT	Reduce triglycerides and increase HDL.
	Red yeast rice	IV, AS	Significant lipid-lowering activity due to multiple mechanisms.
	St Mary's thistle	AS, CT	Possibly due to inhibition of HMG-CoA.
	Taurine	AS	
	Turmeric	AS, CT	Dose-dependent activity exhibited in vivo; activity may be due to increased cholesterol excretion.
	Vitamin B_3	CT	Reduces total cholesterol, LDL, triglycerides and lipoprotein-a levels and also markedly raises HDL levels.
	Vitamin B_5	IV, AS, CT	Mechanism of action relates to reduced insulin resistance and activation of lipolysis in serum and adipose tissue.

Continued

Major actions (known or suspected)	Herb/Nutrient	Evidence	Comments
	Withania	AS	Decreased lipids, cholesterol, triglycerides and MGH-CoA reductase activity.
Anti-atherogenic			
	Andrographis	AS	Significantly improves atherosclerotic iliac artery stenosis induced by both de-endothelialisation and a high-cholesterol diet.
	Dunaliella salina	AS	Anti-atherogenic.
	Garlic	AS, CT	Reduces atherogenic process.
	Oats	IV	Avenanthramides shown to decrease expression of endothelial pro-inflammatory cytokines.
	Olive	IV, AS	Modifies vascular response, inhibits platelet-activating factor, exerts a suppressive effect on the inflammatory response and protects against carotid atherosclerosis.
	Quercetin	AS	Inhibits key molecules involved in early-stage development of atherosclerosis.
	Selenium	AS	Reduces high-fat diet-induced atherosclerosis.
	Turmeric	IV, AS	Anti-atherogenic.
	Vitamin B_3		Anti-atherogenic.
Male fertility			
	Albizia	AS	Significantly reduces fertility in males; reduces weight of testes, epididymides, seminal vesicle and ventral prostate.
	Astragalus	IV	Stimulates sperm motility.
	L-Carnitine	CT	Increases semen quality, sperm concentration and total and forward sperm motility.
	Ginseng — Korean	CT, AS	Activation of cAMP-responsive element modulator in the testes; improves erectile dysfunction.
	Quercetin	AS	Improves sperm motility, viability and concentration; increases weight of testes, epididymis and vas deferens.
	Selenium	CT, AS	Required for human sperm maturation and sperm motility; positive correlation between selenium levels and sperm density, number, motility and viability. Selenium-dependent antioxidant systems imperative in spermatogenesis.
	Tribulus	IV, AS	Androgenic, producing increase in testosterone and DHEA; protodioscin converts to DHEA; observed pro-erectile effects with protodioscin, due to increased release of NO from the endothelium and nitronergic nerve endings; improves spermatogenesis.
	Vitamin C	CT	Antioxidant mechanism.
	Zinc		Deficiency affects spermatogenesis.
Nephroprotection			
	Ginger	AS	Dose dependent.
	Goldenrod	TU	Believed to stabilise the microarchitecture of the kidneys.
	Lycopene	AS	
	St Mary's thistle	IV, AS	
Neuroprotection			
	Baical skullcap	AS, IV	Action attributed to the flavonoid component; baicalein neuroprotective mechanism attributed to increased dopamine and serotonin and inhibition of oxidative stress.

Major actions (known or suspected)	Herb/Nutrient	Evidence	Comments
	Brahmi	AS	
	L-Carnitine	AS	
	Cocoa	IV	Flavonoids, epicatechin and catechin protect from amyloid beta-protein-induced neurotoxicity.
	Coenzyme Q10	AS	Antioxidant capacity protects against neuronal damage.
	Creatine	AS, CT	Various theories and possible mechanisms, including antioxidant capacity and mitochondrial stabilising effects.
	Donq quai	IV, CT	Prevented neurotoxicity induced by A-beta-associated oxidative stress in vitro.
	Evening primrose oil	AS	Regulation of thrombotic and inflammatory mediators.
	Fish oils	CT	
	Folate		Improved NO levels in brain and synthesis of neurotransmitters.
	Ginkgo biloba	IV, AS, CT	Mechanisms of action include antioxidant, membrane stabilisation, platelet-activating factor antagonism, mitochondrial activity and anti-amyloid aggregation effect.
	Ginseng — Korean	IV	Dose-dependent neuroprotective activity in vivo and in vitro.
	Ginseng — Siberian	IV, AS	Appears to protect against neuritic atrophy and cell death under amyloid beta plaque and inhibits the release of NO and neuronal apoptosis.
	Goji	IV, AS	Component arabinogalactan-protein appears to have strongest effect.
	Grapeseed extract	IV, AS	Mediated through antioxidant mechanisms.
	Green tea	IV, AS	Epigallocatechin gallate component.
	Licorice	IV, AS	Mediated though antioxidant, anti-inflammatory and modulation of apoptosis pathways.
	Quercetin		Dose dependent.
	Rhodiola	AS	Dose-dependently protects against oxidative stress-induced apoptosis, inhibits NO and restores mitochondrial function.
	St Mary's thistle	IV, AS	Exhibits protective effect on antioxidant defence systems.
	Schisandra	IV, AS	Enhances cerebral antioxidant status and cholinergic function.
	Shatavari	AS	Attributed to antioxidant mechanisms.
	Vitamin B_1 (thiamin)	AS	Deficiency state impairs blood CSF barrier functionality.
	Vitamin B_3	AS	May be mediated through anti-inflammatory and antioxidant mechanisms.
	Vitamin B_6	IV, AS	Activity may be due to GABA inhibition; protects against glutamate-induced neurotoxicity in vivo.
	Vitamin B_{12}	CT	Possibly due to homocysteine reduction.
	Vitamin C		
	Vitamin D		Increased glutathione and reduced NO production, neuroprotective effects.
	Vitamin E		May be mediated via antioxidant activity.
	Withania	IV, AS	May be mediated via antioxidant activity.

Continued

Major actions (known or suspected)	Herb/Nutrient	Evidence	Comments
Neurotransmitter effects —See listing under Antidepressant			
Reproductive hormonal effects			
	Black cohosh	IV, AS, CT	Reduces level of luteinising hormone. Oestrogenic activity is controversial.
	Chaste tree	IV, CT	Inhibits prolactin release by selective stimulation of pituitary dopamine D_2 receptors; however, low dose may increase secretion. Stimulates progesterone-receptor expression in vitro; competitive binding to oestrogen receptors alpha and beta in vitro.
	Damiana	IV, AS	Weak oestrogen agonist activity reported; possibly works via progesterone receptors; constituent delta-cadinene is reported to be a testosterone inducer and 1,8-cineole a testosterone hydroxylase inducer.
	Dong quai	IV	Weak oestrogen-receptor-binding activity and weak oestrogen-agonistic activity reported.
	Ginseng — Korean	AS	Gonadotrophin-like action; contains phyto-oestrogens.
	Hops	IV	Significant competitive binding to oestrogen receptors alpha and beta and up-regulation of progesterone receptors.
	Licorice	CT	Conflicting results relating to modulation of testosterone levels; isoflavone component exerts mild oestrogen agonist effect; demonstrated oestrogen-like activities.
	Peppermint	AS	Found to increase FSH and LH and reduce total testosterone.
	Pygeum	IV	Effect upon dihydrotestosterone synthesis; androgen antagonistic activity; oestrogenic and anti-oestrogenic.
	Red clover	IV, AS	Attributed to isoflavone content which demonstrates varying levels of oestrogenic activity.
	Rosemary	AS	Anti-oestrogenic.
	Sage oil	IV	Oestrogenic effects.
	SAMe	CT	Reduces prolactin levels.
	Saw palmetto	AS, CT	Inhibits 5-alpha reductase, preventing the conversion of testosterone to dihydrotestosterone; inhibits binding of DHT and testosterone to androgen receptors and inhibits prolactin.
	Shatavari	AS, CT	Oestrogenic effect on mammary glands and genital organs; galactogogue activity exerted by release of corticoids and prolactin.
	Soy	IV, CT	Selective oestrogen-receptor modulator.
	Tea tree oil	IV	Oestrogenic and anti-androgenic activity.
	Tribulus	IV, AS	Androgenic-producing increase in testosterone and DHEA; protodioscin converts to DHEA; observed pro-erectile effects with protodioscin, due to increased release of NO from the endothelium and nitronergic nerve endings; saponins appear to increase FSH in women, generating an increase in oestradiol.
	Wild yam	IV, AS	Conflicting outcomes; may exert oestrogenic and progesteronal activity or anti-oestrogenic and/or anti-androgenic activity.

Major actions (known or suspected)	Herb/Nutrient	Evidence	Comments
Thermogenic effects			
	Ginger	AS	
	Green tea	CT	Interaction between catechin polyphenols and caffeine stimulates noradrenaline release and reduces noradrenaline catabolism.
Thyroid modulation			
	Brahmi	AS	Increases T_4 concentration.
	Fenugreek	AS	Reduces conversion of T_4 to T_3, resulting in increased T_4 concentration.
	Iodine	PH	Essential for manufacture of T_4 and T_3.
	Lemon balm		Inhibits binding of thyroid-stimulating hormone to thyroid plasma membranes and extra-thyroidal enzymic T4-5′-deiodination to T_3.
	SAMe	CT	Possible dopaminergic effects.
	Selenium	CT	Required for normal thyroid hormone synthesis, activation and metabolism.
	Withania	AS	Root extract enhances serum T_4 concentration.
Uterine effects			
	Raspberry leaf	AS	Exerts a regulatory action on uterine contractions.
	Shatavari	AS	Inhibits uterine contraction by competitively blocking the effect of oxytocin; action appears mediated through asparagamine, a polycyclic alkaloid.
Visual function			
	Bilberry	ES, AS	Accelerated modulation of retinal enzyme activity, improved microcirculation and antioxidant effect.
	Quercetin	IV	Inhibits lens aldose reductase by 50%.
	Taurine		Required for pre- and postnatal development of visual system.
	Vitamin A		Retinaldehyde essential component of rhodopsin and retinoic acid maintains normal differentiation of cells in the conjunctiva, cornea and other ocular structures.
Wound healing/enhancement			
	Aloe vera	IV, AS, CT	Inhibits thromboxane, which would normally inhibit wound healing in vitro; improves collagen composition and cross-linking; increases proliferation of human keratinocytes and increases epidermal growth factor and fibronectin.
	Calendula	AS, CT	Due to more intensive metabolism of glycoproteins, nucleoproteins and collagen proteins during regeneration of tissues.
	Chamomile	CT	Significantly improved healing and decreased healing time of excision, incision and burns.
	Chickweed	TU	
	Chitosan	PH	Bacteriostatic effect.
	Echinacea	CT	Topically.
	Gentian	AS	Increases stimulation of collagen production and mitotic activity.

Continued

Major actions (known or suspected)	Herb/Nutrient	Evidence	Comments
	Ginseng — Korean	IV, CT	May enhance cell proliferation, epidermal growth factor, fibronectin, keratin, collagenase and angiogenesis.
	Grapeseed extract	IV, AS	Accelerates wound contraction and closure; resveratrol facilitates oxidant-induced vascular endothelial-growth-factor expression in keratinocytes.
	Honey	AS, CT	Topical use, accelerates wound healing, deodorises wounds and assists in debriding.
	Myrrh	TU	
	St John's wort	TU	May be based on anti-inflammatory, analgesic and anti-microbial activities.
	Slippery elm	TU, PH	High mucilage content.
	Turmeric	AS	Healing associated with regulation of the growth factor TGF-beta-1 and iNOS.
	Vitamin B_2	AS	Deficiency lengthens the time to epithelialisation of wounds, slows the rate of wound contraction and reduces the tensile strength of incision wounds.
	Vitamin B_5	IV, AS	Oral and topical administration shown to accelerate closure of wound and increase strength of scar tissue.
	Vitamin C	IV	
	Vitamin E	IV, CT	Assists in repair of abrasions, burns, grazes and skin lesions.
	Zinc	IV, AS, CT	Essential co-factor in wound healing and immune function.

INDEX