Pharmaceutical Press

Stockley's Herbal Medicines Interactions

Edited by **Elizabeth Williamson, Samuel Driver and Karen Baxter**









Stockley's Herbal Medicines Interactions

Stockley's Herbal Medicines Interactions

A guide to the interactions of herbal medicines, dietary supplements and nutraceuticals with conventional medicines

Editors

Elizabeth Williamson, BSc, PhD, MRPharmS, FLS
Samuel Driver, BSc
Karen Baxter, BSc, MSc, MRPharmS

Editorial Staff

Mildred Davis, BA, BSc, PhD, MRPharmS
Rebecca E Garner, BSc
C Rhoda Lee, BPharm, PhD, MRPharmS
Alison Marshall, BPharm, DipClinPharm, PGCertClinEd, MRPharmS
Rosalind McLarney, BPharm, MSc, MRPharmS
Jennifer M Sharp, BPharm, DipClinPharm, MRPharmS

Digital Products Team

Julie McGlashan, BPharm, DipInfSc, MRPharmS
Elizabeth King, Dip BTEC PharmSci

London • Chicago Pharmaceutical Press

Published by the Pharmaceutical Press
An imprint of RPS Publishing

1 Lambeth High Street, London SE1 7JN, UK
100 South Atkinson Road, Suite 200, Grayslake, IL 60030-7820, USA

First published 2009

Typeset by Data Standards Ltd, Frome, Somerset
Printed in Great Britain by TJ International, Padstow, Cornwall

ISBN 978 0 85369 760 2

A catalogue record for this book is available from the British Library

Contents

Preface

This first edition of *Stockley's Herbal Medicines Interactions* is an exciting new addition to the Stockley family of products, and one that has been several years in the planning and execution. When researching *Stockley's Drug Interactions* we had noticed the growing wealth of experimental data on herbal medicines, which does not fall within the brief of Stockley, which is primarily a clinically based reference work. However, it seemed somewhat of an omission to overlook what is obviously valuable information in what can almost be considered a new field of drug interactions. We therefore reached the point where we decided that it was worth producing a book dedicated to this information; however, little did we realise what a journey we'd be taking ourselves on.

As a group dedicated to the study of drug interactions, and the provision of clinically relevant data (aided by the large number of practising pharmacists we have on our team), we felt well equipped to deal with the interactions data. The herbal medicines side of things was, however, not something that we were particularly familiar with, and we were greatly relieved to be approached by Elizabeth Williamson, with a very similar idea to our own, but with a wealth of knowledge on herbal medicines with which to guide us. Liz is widely published in the field of herbal medicines, and is a member of a number of bodies that consider many aspects of herbal medicine use, such as the British Pharmacopoeia Commission. Liz is the Chair of the Expert Advisory Group for Herbal and Complementary Medicines, which advises the BPC on standards for herbal drugs for the pharmaceutical industry. As a team therefore, we feel we have unrivalled experience in assessing herb–drug interactions, and we believe that ours is a unique collaboration.

Herbal medicines are, more than ever, receiving attention, both from the public and healthcare professionals alike, with many countries now undertaking registration schemes for traditional medicines. However, healthcare professionals still freely admit their lack of knowledge in this area, and surveys suggest that patients often rely on friends and family for advice about herbal medicines. Never has there been a more appropriate time to advise healthcare professionals so that they can provide balanced, helpful advice to patients wishing to take herbal medicines with their 'conventional' treatments. Our aim, as ever, has therefore been to critically evaluate the published literature and present it in a familiar, easy-to-handle format, so that the busy healthcare professional can quickly access the information and apply it to their clinical situation.

This publication attempts to answer the same questions that we address in *Stockley's Drug Interactions*, namely:

- Are the drugs and substances in question known to interact or is the interaction only theoretical and speculative?
- If they do interact, how serious is it?
- Has it been described many times or only once?
- Are all patients affected or only a few?
- Is it best to avoid these two substances altogether or can the interaction be accommodated in some way?
- And what alternative and safer drugs can be used instead?

Stockley's Herbal Medicines Interactions follows the same easy-to-read format as our other publications, with the text organised into a series of individual monographs, all with a common format. In addition, we have included sections on: nomenclature, to help users identify herbal medicines that they or their patients may be familiar with under a different name; uses, so that those less familiar with herbal medicines can put their use into context; and constituents, to allow us to address interactions that occur as a result of a substance common to several plants. A pharmacopoeia section is also included for those herbal medicines, dietary supplements and nutraceuticals that have entries in the latest editions (at time of press) of the *British Pharmacopoeia*, the *European Pharmacopoeia* and the *United States Pharmacopoeia*. An indication of the constituents that the herbal medicine may be standardised for is also provided where necessary, but note that this does not necessarily mean that all marketed products are standardised in this way. In addition, we have added the simple, intuitive ratings system that users of *Stockley's Interaction Alerts* and *Stockley's Drug Interactions Pocket Companion* will already be familiar with.

As with all Stockley products, the text is written for a worldwide audience. Terminology has been carefully considered and international terms have been added where it was thought helpful to do so. This and the inclusion of the synonyms and pharmacopoeia sections will, we hope, cater for the needs of healthcare professionals around the world.

As always, the Editorial team have had assistance from many other people in developing this publication, and the Editors gratefully acknowledge the assistance and guidance that they have provided. Of particular note are: the Digital Products Team led by Jane Macintyre; Ithar Malik, Ruchi Birla, Karl Parsons, Tom Whitaker and Darren Searson, who

have worked tirelessly in transforming our data into a useable output. Particular thanks are also due to the editor of *Martindale*, Sean Sweetman, who has acted as our mentor on a number of other projects, and continues to provide invaluable support. Thanks are also due to Tamsin Cousins, who has handled the various aspects of producing this publication in print. We are also grateful for the support of both Paul Weller and Charles Fry. Ivan Stockley remains an important part of all products bearing his name, and we are most grateful for the feedback that he provided on this new project.

Stockley's Herbal Medicines Interactions is available on the Pharmaceutical Press platform, *MedicinesComplete*, and we are indebted to Julie McGlashan and Elizabeth King, and all those involved in the development of these products, for their advice and support. For more details about these digital products please visit: www.pharmpress.com/Stockley

We are always interested in hearing feedback from users of our publications, and have in the past received many useful comments, which help us to develop the product to best meet the needs of the end-user. Anyone who wishes to contact us can do so at the following address: stockley@rpsgb.org

Sam Driver, Karen Baxter and Elizabeth Williamson
London, February 2009

Abbreviations

ACE	angiotensin-converting enzyme
ADP	adenosine diphosphate
AIDS	acquired immune deficiency syndrome
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC	area under the time–concentration curve
$AUC_{0\text{-}12}$	area under the time–concentration curve measured over 0 to 12 hours
AV	atrioventricular
BCRP	breast cancer resistance protein
BP	blood pressure
BP	British Pharmacopoeia
bpm	beats per minute
CNS	central nervous system
COX	cyclo-oxygenase
CSF	cerebrospinal fluid
CSM	Committee on Safety of Medicines (UK) (now subsumed within the Commission on Human Medicines)
ECG	electrocardiogram
ECT	electroconvulsive therapy
e.g.	exempli gratia (for example)
EMEA	The European Agency for the Evaluation of Medicinal Products
FDA	Food and Drug Administration (USA)
FSH	follicle-stimulating hormone
g	gram(s)
HAART	highly active antiretroviral therapy
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
ibid	*ibidem*, in the same place (journal or book)
i.e.	id est (that is)
INR	international normalised ratio
IU	international units
IUD	intra-uterine device
kg	kilogram(s)
L	litre(s)
LDL	low-density lipoprotein
LFT	liver function test
LH	luteinising hormone
LMWH	low-molecular-weight heparin
MAC	minimum alveolar concentration
MAO	monoamine oxidase
MAOI	monoamine oxidase inhibitor
MHRA	Medicines and Healthcare products Regulatory Agency (UK)
MIC	minimum inhibitory concentration
mEq	milliequivalent(s)
mg	milligram(s)
mL	millilitre(s)
mmHg	millimetre(s) of mercury
mmol	millimole
mol	mole
nmol	nanomole
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
NSAID	non-steroidal anti-inflammatory drug
OATP	organic anion transporting polypeptide
PCP	pneumocystis pneumonia
pH	the negative logarithm of the hydrogen ion concentration
Ph Eur	European Pharmacopoeia, 6th ed., 2008 and Supplements 6.1, 6.2, 6.3 and 6.4
PPI	proton pump inhibitor
ppm	parts per million
PTT	partial thromboplastin time
sic	written exactly as it appears in the original
SNRI	serotonin and noradrenaline reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor
TSH	thyroid-stimulating hormone
UK	United Kingdom
USP	The United States Pharmacopeia
US and USA	United States of America
WHO	World Health Organization

General considerations

Structure of the publication

The basic issues involved in assessing the importance of interactions between herbal medicines (which for the purposes of this book are also taken to include nutritional supplements and some items of food) and drugs are similar to those for interactions between conventional drugs, but for herbal medicines the picture is complicated by their very nature: they are complex mixtures themselves and there is also a lack of reliable information about their occurrence and relevance.

Before using this publication it is advisable to read this short explanatory section so that you know how the drug interaction data have been set out here, and why, as well as the basic philosophy that has been followed in presenting it.

The monographs

This publication includes over 150 herbal medicines, nutraceuticals or dietary supplements. For each of these products there is an introductory section, which includes the following sections where appropriate:

- Synonyms and related species or Types, sources and related compounds
- Pharmacopoeias
- Constituents
- Uses and indications
- Pharmacokinetics
- Interactions overview.

The synonyms, constituents and uses have largely been compiled with reference to a number of standard sources. These include:

- Sweetman SC (ed), *Martindale: The Complete Drug Reference 36*. [online] London: Pharmaceutical Press http://www.medicinescomplete.com/
- Williamson EM, ed. Potter's Herbal Cyclopaedia. Saffron Walden: The C.W. Daniel Company Limited; 2003.
- Barnes J, Anderson LA, Phillipson JD (eds), *Herbal Medicines 3*. [online] London: Pharmaceutical Press http://www.medicinescomplete.com/
- Williamson EM, ed. Major Herbs of Ayurveda. 1st ed. London: Elsevier; 2002.

More than 550 interactions monographs are included, each with a common format. These are subdivided into the following sections:

- Abstract or summary for quick reading.
- Clinical evidence, detailing the interaction and citing the clinical evidence currently available.
- Experimental evidence. Due to the nature of interactions with herbal medicines much of the data currently available comes from *animal* and *in vitro* studies. Although this data doesn't always extrapolate to the clinical situation it can be used to provide some idea of the likelihood and potential severity of an interaction. It has been deliberately kept separate from the clinical data, because this type of data is a better guide to predicting outcomes in practice.
- Mechanism, to allow an understanding as to why the interaction may occur.
- Importance and management. As with all Stockley products, providing guidance on how to manage an interaction is our key aim. The short discussion is designed to aid rapid clinical decision-making.
- References, a list of all of the relevant references.

Some of the monographs have been compressed into fewer subsections instead of the more usual five, simply where information is limited or where there is little need to be more expansive.

The monographs also carry an adapted form of the drug interaction Hazard/Severity ratings as used in the electronic *Stockley Interactions Alerts* and *Stockley's Drug Interactions Pocket Companion*. Where difficulties arise in applying ratings to monographs that cover multiple pairs of drug–herb interactions, we have chosen to illustrate the worst-case scenario. Reading the Importance and management section will explain which members of the groups are most likely to represent a problem.

The interactions are rated using three separate categories:

- Action: this describes whether or not any action needs to be taken to accommodate the interaction. This category ranges from 'avoid' to 'no action needed'.
- Severity: this describes the likely effect of an unmanaged interaction on the patient. This category ranges from 'severe' to 'nothing expected'.
- Evidence: this describes the weight of evidence behind the interaction. This category ranges from 'extensive' to 'theoretical, weak'.

These ratings are combined to produce one of five symbols:

 For interactions that have a life-threatening outcome, or where concurrent use is considered to be best avoided.

 For interactions where concurrent use may result in a significant hazard to the patient and so dosage adjustment or close monitoring is needed.

For interactions where there is a potentially hazardous outcome, but where, perhaps, the data is poor and conclusions about the interaction are difficult to draw.

For interactions where there is doubt about the outcome of concurrent use, and therefore it may be necessary to give patients some guidance about possible adverse effects, and/or consider some monitoring.

For interactions that are not considered to be of clinical significance, or where no interaction occurs.

We put a lot of thought in to the original design of these symbols, and have deliberately avoided a numerical or colour-coding system as we did not want to imply any relationship between the symbols and colours. Instead we chose internationally recognisable symbols, which in testing were intuitively understood by our target audience of healthcare professionals.

There are also several 'family monographs' included. These are for constituents that have been demonstrated to interact in their own right, but which are prevalent in a number of herbal medicines, the most common example of this being the flavonoids. This structure allows us to assess the relevant data in one place, and cross-reference the reader as appropriate. Because so many herbs contain a multitude of these constituents it would not be possible to cover them in each plant monograph.

Data selection

This publication has been produced by the team that writes *Stockley's Drug Interactions*, with the help and guidance of an expert in the herbal medicines field. The same rigorous approach that is used to produce *Stockley's Drug Interactions* has been applied here, although with some notable differences, particularly in the selection of data for inclusion. The data on interactions are of widely varying quality and reliability, and this is even more the case when considering interactions between herbal medicines and conventional drugs. The best information comes from clinical studies carried out on large numbers of patients under scrupulously controlled conditions; however, with herbal medicines these are sparse. Indeed those that there are have already been included in *Stockley's Drug Interactions*. What this publication attempts to do is assess the wealth of data from *animal* and *in vitro* studies, which would not normally be considered for inclusion in *Stockley's Drug Interactions*.

As with all our publications we undertake extensive literature searching, we consider guidance published by regulatory bodies and we aim to avoid citing secondary literature wherever possible. Some of the studies cited in herb–drug interaction articles or publications are of doubtful quality and some are merely speculation. We have included them because they appear in other reference sources for interactions, but we have attempted to put their results and recommendations in perspective.

The herbal medicines, dietary supplements and nutraceuticals selected for inclusion in this first edition were chosen on the basis of their popularity and/or because they have interaction reports associated them.

Nomenclature

Every care has been taken to correctly identify the herbal medicine involved in interactions. The botanical nomenclature and the vast number of colloquial names used for the plants can be very confusing. We have therefore adopted one name for each herbal medicine that is used consistently throughout the monograph, and indeed across the publication. However, we are aware that we will not always have selected the most appropriate name for some countries and have therefore included a synonyms field to aid users who know the plant by different names. The synonyms come from several well-respected sources and, where botanical names are used, have been cross-checked against the extremely useful database constructed by Kew (Royal Botanic Gardens, Kew (2002). electronic Plant Information Centre. Available at http://epic.kew.org/epic/). Occasionally the same synonym has been used for more than one herbal medicine and, where we are aware of this, we have been careful to highlight the potential for confusion.

We should also point out that we have chosen the phrase 'conventional medicines' to distinguish those products that are licensed and commonly used in Western medicine. This nomenclature is not meant to imply any preference, it is just simply a way of being clear about which preparation we are discussing.

Similarly, there is the potential for confusion between the synthetic coumarins used as anticoagulants (e.g. warfarin, acenocoumarol) and those coumarins that occur naturally within plants. We have therefore chosen to use the term 'coumarins' for those of synthetic origin, and 'natural coumarins' to distinguish those of plant origin.

Incidence of herbal medicines interactions

The incidence of interactions between herbal medicines and nutritional supplements with conventional drugs is not yet fully known, and there is no body of reliable information currently available to draw upon when assessing the scale of any possible problem, or predicting clinical outcomes. Even in the case of St John's wort, which is now commonly known to interact with a number of drugs, the clinical significance of some reported cases cannot be accurately evaluated due to the variation in the nature of the herb itself and products made from it. In general, the lack of evidence may be due to under-reporting or unrecognised interactions, but there is also the possibility that many herbal medicines have a generally safe profile and do not interact significantly with drugs. Given the poor quality of information available it can be difficult to put the problem into perspective and in the absence of good evidence, speculation has taken its place. Ivan Stockley, a pioneer in the field of drug-interaction investigation, has often maintained that data on interactions are of widely varying quality and reliability, and stated that 'sometimes they are no more than speculative and theoretical scaremongering guesswork, hallowed by repeated quotation until they become virtually set in stone'. Although these remarks were made in the context of drug interactions, they are even more apposite when applied to herb–drug interactions where anecdotal reports, uncontrolled studies or data based solely on *animal* studies are the main form of evidence available. These have to be evaluated very carefully before advising patients as to the safety (or not) of combining herbal medicines with either other supplements or conventional drugs. While many publications uncritically use theoretical evidence to advise on this issue, it risks the danger that patients (and their friends and families) who have

already taken supplements and drugs together with no problems will no longer believe even good advice – and subsequently take incompatible combinations to ill effect. It is also noticeable that, whilst anecdotal or theoretical evidence is quite rightly considered unacceptable as evidence of efficacy for herbal products, it seems to be given undue credibility when demonstrating toxicity, and consumers of natural medicines have observed this double standard. Obviously the best answer to this problem is for good and reliable evidence to become available, and for the importance of reports to be based on the nature of the evidence that they provide. In the first instance, it would be most useful to know the extent of the problem and the risk or likelihood of a herb–drug interaction arising. However, even numbers of people taking supplements is not accurately known, although over the past 10 years several studies have been carried out to try to assess this. Some knowledge of not only who, but how and why people are taking herbal medicines can help to identify potential problems or warn of them before they arise.

Who uses herbal medicines?

The use of herbal medicines and nutritional supplements is increasing dramatically in many parts of the world, especially in Europe, the US and Australasia, as part of the popularity of complementary and alternative medicine (CAM). It is difficult to measure the extent of the use of herbal products by consumers and patients in a largely unregulated market, especially with so many herbal products being sold over the internet, and survey studies that have attempted to do so have often been criticised for flawed methodology. However, there is no doubt that the issue of people taking herbal and nutritional products at the same time as conventional medicines is significant, and the purpose of this publication is to provide information so that this practice can be carried out as safely as possible.

Some idea of the size of the market and its recent growth can be seen from a series of studies carried out over the past few years in the US. In 1997, the results of a national survey[1] indicated that approximately 12% of the adult responders had taken a herbal remedy in the past year, which was an increase of 380% from 1990, and almost 1 in 5 of those taking prescription drugs were also taking a herbal or vitamin supplement. In 1998 and 1999, a survey of over 2500 adults estimated that 14% of the general population were regularly taking herbal products and, of patients taking prescription drugs, 16% also took a herbal supplement.[2] Data obtained from a separate 1999 survey estimated that 9.6% of US adults used herbal medicines,[3] which was lower than would be expected from the previous study, and illustrates the problems of assessing consumer behaviour accurately, but it is still a significant increase from the 1990 figures. By 2002, figures showed that the annual use of dietary supplements had risen to 18.8%.[4] Although the accuracy of these figures can be questioned, what is also noteworthy is that the studies were carried out in the general population, so it is logical to assume that in the patient population usage could be even higher.

A survey undertaken in the UK in 1994 suggests that the prevalence of alternative medicine use (which included herbal medicines) was 8.5% of the population, whereas in Germany, in 1996, it was much higher, at 65%. The low figure for the UK could be because of national differences, because different types of use were assessed (1-year versus lifetime) or because, at the time, the UK was undergoing a difficult economic period and usually CAM is paid for privately.[5] Useful information about herbal medicinal use can also be obtained from the monetary value of the market. In 2002, French health insurance paid $91 million in partial reimbursements for ginkgo, saw palmetto and pygeum prescriptions, with a total value of $196 million, and, in 2003, German health insurance paid $283 million in reimbursements for prescribed herbal products including ginkgo, St John's wort, saw palmetto, hawthorn, stinging nettle root and pumpkin seed. These figures do not include non-prescription purchase of herbal remedies, but it is known that, in 2003, European countries spent almost $5 billion (at manufacturers' prices) on non-prescription herbal medicines,[6] and of course the cost at consumer level would be very much higher.

1. Eisenberg DM, Davis RB, Ettner SL, Appel S, Wilkey S, Van Rompay M, Kessler RC. Trends in alternative medicine use in the United States, 1990-1997: results of a follow-up national survey. *JAMA* (1998) 280, 1569–75.
2. Kaufman DW, Kelly JP, Rosenberg L, Anderson TE, Mitchell AA. Recent patterns of medication use in the ambulatory adult population of the United States. The Slone Survey. *JAMA* (2002) 287, 337–44.
3. Ni H, Simile C, Hardy AM. Utilization of complementary and alternative medicine by United States adults: results from the 1999 national health interview survey. *Med Care* (2002) 40, 353–8.
4. Kelly JP, Kaufman DW, Kelley K, Rosenberg L, Anderson TE, Mitchell AA. Recent trends in use of herbal and other natural products. *Arch Intern Med* (2005) 165, 281–6.
5. Ernst E. Prevalence of use of complementary/alternative medicine – a systematic review. *Bull WHO* (2000) 78, 252–7.
6. De Smet PAGM. Herbal Medicine in Europe – Relaxing Regulatory Standards. *N Engl J Med* (2005) 352, 1176–8.

Herbal medicine use in specific patient groups

(a) Cancer patients

Certain groups of patients are known, or thought to have, a higher incidence of supplement usage than others. It is generally thought that cancer patients, for example, have an exceptionally high intake of herbal and nutritional supplements. One of the first studies to collate the information available on CAM use in cancer patients was from 1998, when a systematic review of 26 surveys from 13 countries was published. CAM use in adults ranged from 7 to 64%, with an average use of 31.4%.[1] The high degree of variability was thought to be most likely due to different understandings of the term CAM on the part of both investigators and patients, but also illustrates that the results of such surveys must be interpreted very carefully. A subsequent study showed that CAM use (both self-medication and visits to CAM practitioners) had increased significantly from 1998 to 2005 in cancer patients, and it was estimated that more than 80% of all women with breast cancer use CAM, 41% in a specific attempt to manage their breast cancer. The most commonly used herbal products for this purpose in 2005 were flaxseed, green tea and vitamins (C and E).[2] A US survey of outpatients with cancer found that 83.3% had used at least one CAM. Vitamins and herbal medicines were used by 62.6% of patients, and use was greater in women and those of a younger age.[3] These findings were reflected in a 2005 study which confirmed that, of the chemotherapy patients surveyed, 91% reported using at least one form of CAM (most frequently diets, massage and herbal medicine). Of these patients only 57%

discussed the use of at least one of these therapies with their healthcare provider.[4]

Herbal medicine use by cancer patients seems to be high in many parts of the world: in New Zealand 49% of cancer patients at a regional centre used CAM (most commonly vitamins, antioxidants, alternative diets and herbal medicines) to improve the quality of life and in the hope of a cure (47% and 30% of CAM users, respectively). CAM was deemed helpful in the management of their cancer by 71% of patients, and 89% felt that CAM was safe. Younger patients tended to use CAM more.[5] The different patterns of herbal use between cancer patients undergoing palliative or curative chemotherapy has also been studied, and the results confirmed that both groups frequently use herbal remedies concurrently with chemotherapy (37% and 38%, respectively), but with a slightly different intent. Palliative patients tended to show more frequent herbal use than curative patients (78% versus 67%), whereas curative patients used herbal remedies much more often to relieve adverse effects (31% versus 3%).[6]

(b) Patients on weight-loss programmes

Other groups of patients known to use supplements regularly are those on weight-loss programmes and most of the weight-loss supplements taken (73.8%) contained stimulants such as ephedra, caffeine and/or bitter orange. An estimated 15.2% of American adults (women 20.6%, men 9.7%) had used a weight-loss supplement at some time: 8.7% within the past year (women 11.3%, men 6%). Women aged 18 to 34 years used weight-loss supplements the most (16.7%), and use was equally prevalent among ethnic groups and education levels. More worryingly, many adults were long-term users and most did not discuss this practice with their doctor.[7]

(c) Hospital inpatients

A study of herbal medicine use during perioperative care identified the most commonly used medications and assessed their potential for causing adverse events or drug interactions in patients who were having surgical procedures. Their conclusions were that certain herbal medicines posed a potential danger in perioperative care (such as St John's wort because of its enzyme-inducing effects and valerian because of its sedative effects), but no attempt was made to ascertain the incidence of such events.[8] However, in 2007, a study of 299 patients on the medical wards of two hospitals in Israel found that 26.8% of participants took herbal medicines or dietary supplements and, of these, potential interactions were noted in 7.1%. The authors suggested that most patients are not asked specifically about herbal consumption by their medical team.[9]

1. Ernst E, Cassileth BR. The prevalence of complementary/alternative medicine in cancer: a systematic review. *Cancer* (1998) 83, 777–82.
2. Boon HS, Olatunde F, Zick SM. Trends in complementary/alternative medicine use by breast cancer survivors: comparing survey data from 1998 and 2005. *BMC Womens Health* (2007) 7, 4.
3. Richardson MA, Sanders T, Palmer JL, Greisinger A, Singletary SE. Complementary/alternative medicine use in a comprehensive cancer center and the implications for oncology. *J Clin Oncol* (2000) 18, 2505–14.
4. Yates JS, Mustian KM, Morrow GR, Gillies LJ, Padmanaban D, Atkins JN, Issell B, Kirshner JJ, Colman LK. Prevalence of complementary and alternative medicine use in cancer patients during treatment. *Support Care Cancer* (2005) 13, 806–11.
5. Chrystal K, Allan S, Forgeson G, Isaacs R. The use of complementary/alternative medicine by cancer patients in a New Zealand regional cancer treatment centre. *N Z Med J* (2003) 116, U296.
6. Engdal S, Steinsbekk A, Klepp O, Nilsen OG. Herbal use among cancer patients during palliative or curative chemotherapy treatment in Norway. *Support Care Cancer* (2008) 16, 763–9.
7. Blanck HM, Serdula MK, Gillespie C, Galuska DA, Sharpe PA, Conway JM, Khan LK, Ainsworth BE. Use of nonprescription dietary supplements for weight loss is common among Americans. *J Am Diet Assoc* (2007) 107, 441–7.
8. Ang-Lee MK, Moss J, Yuan C-S. Herbal medicines and perioperative care. *JAMA* (2001) 286, 208–16.
9. Goldstein LH, Elias M, Ron-Avraham G, Biniaurishvili BZ, Madjar M, Kamargash I, Braunstein R, Berkovitch M, Golik A. Consumption of herbal remedies and dietary supplements amongst patients hospitalized in medical wards. *Br J Clin Pharmacol* (2007) 64, 373–80.

Differences in herbal use in specific population groups

(a) The elderly

CAM use is high in those of 65 years of age and over (27.7% according to one US study), but declines among those aged 75 years and over and, overall, more women than men are CAM users. The highest level of use seems to be among Asians (48.6%), followed by Hispanics (31.6%), whites (27.7%) and blacks (20.5%).[1] Data drawn from a 2002 survey that included a supplement on the use of herbal medicines, with the analysis limited to adults aged 65 years and older, showed that herbs were an important component of their own health management. Whereas about 25% of the Asian and Hispanic elderly used herbal medicines, only about 10% of the black and white elderly used them; the herbs used, and the reasons for doing so, also differed according to ethnicity.[2]

It is also apparent that, in the elderly, the use of herbal medicines with conventional medicines, both prescription and non-prescription, is widespread. The risk for adverse interactions was assessed in a Medicare population, using a retrospective analysis of Cardiovascular Health Study interview data from four different years. Of 5052 participants, the median age at the beginning of the study was 75 years, 60.2% were female, 16.6% were African–American and 83.4% were white. From 1994 to 1999 the number using herbal medicines increased from 6.3% to 15.1%, and the number using herbal medicines concurrently with conventional drugs also increased, from 6% to 14.4%. Combinations thought to be potentially risky were noted in 393 separate interviews, with most (379 reports in 281 patients) involving a risk of bleeding due to use of garlic, ginkgo or ginseng together with aspirin, warfarin, ticlopidine or pentoxifylline. An additional 786 drug–herb combinations were considered to have some (again) theoretical or uncertain risk for an adverse interaction.[3]

The type of products taken obviously reflect the age group taking them, and the most common products used by the elderly are those concerned with ameliorating degenerative or age-related conditions. In a predominantly white (91%) elderly cohort, the use of dietary supplements was surveyed each year from 1994 to 1999 for an average of 359 male (36%) and female (64%) participants aged 60 to 99 years. By 1999, glucosamine emerged as the most frequently used (non-vitamin, non-mineral) supplement followed by ginkgo, chondroitin and garlic. For women, there was a significant trend of increasing use for black cohosh, starflower oil, evening primrose oil, flaxseed oil, chondroitin, prasterone (dehydroepiandrosterone), garlic, ginkgo, glucosamine, grapeseed extract, hawthorn and St John's wort. For men, alpha-lipoic acid, ginkgo and grapeseed extract showed a similar trend.[4]

(b) Children

Surprisingly, herbal medicine and nutritional supplement use in children can also be high, and so is the concurrent use with conventional medicine. A convenience sampling of paediatric emergency department patients in the US was carried out during a 3-month period in 2001, where 153 families participated in the study, with a mean patient age of 5.3 years. Children were given a herbal medicine by 45% of caregivers, and the most common herbal medicines reportedly used were aloe plant or juice (44%), echinacea (33%) and sweet oil (25%).[5]

More recently, 1804 families were interviewed in a study of parents and patients up to 18 years arriving at a large paediatric emergency department in Toronto, Canada. Conventional and herbal medicines or supplements were being used concurrently in 20% of the patients and 15% were receiving more than one herbal medicine simultaneously. The authors of this study identified possible herb–drug or herb–herb interactions in 16% of children.[6]

(c) Gender

Studies usually show that herbal medicine use is higher in women than men, and this is likely to be true for many reasons, despite the unreliability of figures gained in surveys. Women generally live longer than men, and elderly people take more supplements; women tend to be the primary carers for children and the elderly and also purchase most of the everyday remedies used in the home; and women take more weight-loss products than men. In several studies, it is suggested that women are at least twice as likely to take herbal medicines or supplements as men.[1,7-10]

(d) Educational level and knowledge of herbal products

People of all levels of educational attainment are likely to take herbal and nutritional supplements. Some studies suggest that usage is similar across most education levels,[10] whereas others have found that college graduates appear to have the highest incidence of herbal use.[4,7,11] Despite the generally high levels of education, it is of great concern that consumers do not have a correspondingly high level of knowledge about the products that they are consuming. In a study of caregivers who reported giving their child a herbal product, 88% had at least 1 year of college education. However, 77% of the participants in the study did not believe, or were uncertain, if herbal medicines had any adverse effects; only 27% could name a potential adverse effect and 66% were unsure, or thought that herbal medicines did not interact with other medications.[5] In a study in Israel of users of 'natural drugs', 56.2% believed that they caused no adverse effects.[12] In Australia, the perceptions of emergency department patients towards CAM were assessed by comparing the CAM users (68% of the patients surveyed) with non-users, particularly regarding safety and efficacy. In both cases there was no significant difference between CAM users and non-users, with 44.1% agreeing that CAM is drug free and, more worryingly, 28.5% agreeing, or strongly agreeing, that CAM is always safe to take with prescription drugs. However, significantly more CAM users agreed that CAM is safe and can prevent people from becoming ill and, furthermore, is more effective than prescription drugs. Moreover, significantly fewer CAM users agreed that prescription drugs are safe to take.[13]

(e) Rural populations

An Australian postal questionnaire survey found that in people living in rural areas of New South Wales the use of CAM is high, with garlic and echinacea being the most used herbal products. Of those responding, 70.3% reported using one or more CAM and 62.7% had visited a complementary practitioner.[14] In Jamaica, concurrent surveys were carried out in Kingston (an urban parish) and Clarendon (a rural parish) in 743 patients who visited health centres and pharmacies. Herbal medicines were taken with conventional medicines by 80% of respondents and 87% of these did not tell their healthcare provider. In the rural community 92% took herbal medicines with conventional medicines, compared with 70% of the urban community.[15]

1. Arcury TA, Suerken CK, Grzywacz JG, Bell RA, Lang W, Quandt SA. Complementary and alternative medicine use among older adults: ethnic variation. *Ethn Dis* (2006) 16, 723–31.
2. Arcury TA, Grzywacz JG, Bell RA, Neiberg RH, Lang W, Quandt SA. Herbal remedy use as health self-management among older adults. *J Gerontol B Psychol Sci Soc Sci* (2007) 62, S142–9.
3. Elmer GW, Lafferty WE, Tyree PT, Lind BK. Potential interactions between complementary/alternative products and conventional medicines in a Medicare population. *Ann Pharmacother* (2007) 41, 1617–24.
4. Wold RS, Lopez ST, Yau CL, Butler LM, Pareo-Tubbeh SL, Waters DL, Garry PJ, Baumgartner RN. Increasing trends in elderly persons' use of nonvitamin, nonmineral dietary supplements and concurrent use of medications. *J Am Diet Assoc* (2005) 105, 54–63.
5. Lanski SL, Greenwald M, Perkins A, Simon HK. Herbal therapy use in a pediatric emergency department population: expect the unexpected. *Pediatrics* (2003) 111, 981–5.
6. Goldman RD, Rogovik AL, Lai D, Vohra S. Potential interactions of drug-natural health products and natural health products-natural health products among children. *J Pediatr* (2008) 152, 521–6.
7. Schaffer DM, Gordon NP, Jensen CD, Avins AL. Nonvitamin, nonmineral supplement use over a 12-month period by adult members of a large health maintenance organization. *J Am Diet Assoc* (2003) 103, 1500–5.
8. Richardson MA, Sanders T, Palmer JL, Greisinger A, Singletary SE. Complementary/alternative medicine use in a comprehensive cancer center and the implications for oncology. *J Clin Oncol* (2000) 18, 2505–14.
9. Yates JS, Mustian KM, Morrow GR, Gillies LJ, Padmanaban D, Atkins JN, Issell B, Kirshner JJ, Colman LK. Prevalence of complementary and alternative medicine use in cancer patients during treatment. *Support Care Cancer* (2005) 13, 806–11.
10. Blanck HM, Serdula MK, Gillespie C, Galuska DA, Sharpe PA, Conway JM, Khan LK, Ainsworth BE. Use of nonprescription dietary supplements for weight loss is common among Americans. *J Am Diet Assoc* (2007) 107, 441–7.
11. Kelly JP, Kaufman DW, Kelley K, Rosenberg L, Anderson TE, Mitchell AA. Recent trends in use of herbal and other natural products. *Arch Intern Med* (2005) 165, 281–6.
12. Giveon SM, Liberman N, Klang S, Kahan E. Are people who use 'natural drugs' aware of their potentially harmful side effects and reporting to family physician? *Patient Educ Couns* (2004) 53, 5–11.
13. Taylor DMD, Walsham N, Taylor SE, Wong LF. Complementary and alternative medicines versus prescription drugs: perceptions of emergency department patients. *Emerg Med J* (2006) 23, 266–8.
14. Wilkinson JM, Simpson MD. High use of complementary therapies in a New South Wales rural community. *Aust J Rural Health* (2001) 9, 166–71.
15. Delgoda R, Ellington C, Barrett S, Gordon N, Clarke N, Younger N. The practice of polypharmacy involving herbal and prescription medicines in the treatment of diabetes mellitus, hypertension and gastrointestinal disorders in Jamaica. *West Indian Med J* (2004) 53, 400–5.

Attitudes to the use of herbal medicines

People who use herbal medicines and nutritional supplements report their primary source of information as friends or relatives in 80% of cases, and only 45% of those giving their children herbal products report discussing it with either their doctor or pharmacist.[1] In one study, 44.7% never reported herbal usage to their physician, and 11% did so only rarely.[2] Again, this is a general trend found in other studies,[3] sometimes with even higher levels (e.g. up to 70%) of non-reporting seen.[4] In one study in New Zealand only 41% of patients had discussed their CAM use with their oncologist, and almost one-third had started such medicines before being seen at the cancer treatment centre.[5] In a study of hospital inpatients a great cause for concern was that 94% of the patients had not been asked specifically about herbal

consumption by the medical team and only 23% of the hospital's medical files of the patients taking herbal medicines or dietary supplements had any record of this fact.[6] In fact, in many studies, even where the question was asked, many patients did not inform their doctor that they were also taking herbal remedies.[7,8]

This serious under-reporting by patients may probably be because they consider herbal medicines safe, even if taken at the same time as prescription drugs.[9] One study found a significant correlation between the belief that herbal medicines can cause adverse effects and the tendency to report their usage to the family physician.[2] Some patients may fear the disapproval of the physician and, since they consider the medicines to be safe, see no reason for inviting problems by disclosing these practices. Unfortunately, even if patients do report their use of herbal medicines to the physician or pharmacist, there is no guarantee that accurate information or advice will be available. Physicians usually underestimate the extent to which their patients use these remedies and often do not ask for information from the patient. Worse still, in one survey 51% of doctors believed that herbal medicines have no or only mild adverse effects and 75% admitted that they had little or no knowledge about what they are.[10] Pharmacists are equally likely to encounter patients taking supplements together with prescription or non-prescription medicines as they may be asked for advice, or they may actually sell or supply the herbal medicine. Many pharmacists (like many doctors) do not feel that they have enough basic knowledge themselves, or information readily available, to recommend these safely,[11] although, according to a study in an international cohort of pharmacists, 84% have tried CAM at some time in their life, and 81% still felt that they had inadequate skills and knowledge to counsel patients.[12] Personal use of dietary supplements was found to correlate with a twofold increase in the likelihood that a pharmacist would recommend them to a patient.[11]

1. Lanski SL, Greenwald M, Perkins A, Simon HK. Herbal therapy use in a pediatric emergency department population: expect the unexpected. *Pediatrics* (2003) 111, 981–5.
2. Giveon SM, Liberman N, Klang S, Kahan E. Are people who use 'natural drugs' aware of their potentially harmful side effects and reporting to family physician. *Patient Educ Couns* (2004) 53, 5–11.
3. Wold RS, Lopez ST, Yau CL, Butler LM, Pareo-Tubbeh SL, Waters DL, Garry PJ, Baumgartner RN. Increasing trends in elderly persons' use of nonvitamin, nonmineral dietary supplements and concurrent use of medications. *J Am Diet Assoc* (2005) 105, 54–63.
4. Blanck HM, Serdula MK, Gillespie C, Galuska DA, Sharpe PA, Conway JM, Khan LK, Ainsworth BE. Use of nonprescription dietary supplements for weight loss is common among Americans. *J Am Diet Assoc* (2007) 107, 441–7.
5. Chrystal K, Allan S, Forgeson G, Isaacs R. The use of complementary/alternative medicine by cancer patients in a New Zealand regional cancer treatment centre. *N Z Med J* (2003) 116, U296.
6. Goldstein LH, Elias M, Ron-Avraham G, Biniaurishvili BZ, Madjar M, Kamargash I, Braunstein R, Berkovitch M, Golik A. Consumption of herbal remedies and dietary supplements amongst patients hospitalized in medical wards. *Br J Clin Pharmacol* (2007) 64, 373–80.
7. Engdal S, Steinsbekk A, Klepp O, Nilsen OG. Herbal use among cancer patients during palliative or curative chemotherapy treatment in Norway. *Support Care Cancer* (2008) 16, 763–9.
8. Delgoda R, Ellington C, Barrett S, Gordon N, Clarke N, Younger N. The practice of polypharmacy involving herbal and prescription medicines in the treatment of diabetes mellitus, hypertension and gastrointestinal disorders in Jamaica. *West Indian Med J* (2004) 53, 400–5.
9. Taylor DMD, Walsham N, Taylor SE, Wong LF. Complementary and alternative medicines versus prescription drugs: perceptions of emergency department patients. *Emerg Med J* (2006) 23, 266–8.
10. Giveon SM, Liberman N, Klang S, Kahan E. A survey of primary care physicians' perceptions of their patients' use of complementary medicine. *Complement Ther Med* (2003) 11, 254–60.
11. Howard N, Tsourounis C, Kapusnik-Uner J. Dietary supplement survey of pharmacists: personal and professional practices. *J Altern Complement Med* (2001) 7, 667–80.
12. Koh HL, Teo HH, Ng HL. Pharmacists' patterns of use, knowledge, and attitudes toward complementary and alternative medicine. *J Altern Complement Med* (2003) 9, 51–63.

Interactions between herbal medicines and conventional drugs

An interaction is said to occur when the effects of one drug are changed by the presence of another substance, including herbal medicines, food, drink and environmental chemical agents.

This definition is obviously as true for conventional medicines as it is for herbal medicines. The outcome can be harmful if the interaction causes an increase in the toxicity of the drug. A potential example of this is the experimental increase in toxicity seen when amikacin is given with ginkgo, see Ginkgo + Aminoglycosides, page 209. A reduction in efficacy due to an interaction can sometimes be just as harmful as an increase. For example, the reduction in ciclosporin levels caused by St John's wort has led to transplant rejection in some cases. See St John's wort + Ciclosporin, page 368.

As with any publication detailing the adverse effects of drug use it would be very easy to conclude after browsing through this publication that it is extremely risky to treat patients with conventional drugs and herbal medicines, but this would be an over-reaction. Patients can apparently tolerate adverse interactions remarkably well, and many interactions can be accommodated for (for example, through natural dose titration), so that the effects may not consciously be recognised as the result of an interaction.

One of the reasons that it is often difficult to detect an interaction is that, as already mentioned, patient variability is considerable. We now know many of the predisposing and protective factors that determine whether or not an interaction occurs but in practice it is still very difficult to predict what will happen when an individual patient is given two potentially interacting medicines. This effect is compounded when considering the interactions of herbal medicines because they themselves are subject to a degree of variability.

Variability of herbal medicines

Botanical extracts differ from conventional medicines in that they are complicated mixtures of many bioactive compounds. This makes it difficult to assess the contribution of each constituent to the activity of the whole, and this includes evaluating their possible interactions with drugs. Natural products are also liable to a great deal of variation and, even when standardised to one of more of their constituents, there can still be differences in the numerous other compounds present, and different constituents will affect different metabolic enzymes. As well as the source material, the method by which an extract is made will also affect its composition, and thus its interaction potential. This is well illustrated by a study looking at echinacea preparations. This study found that a standardised Swiss-registered *Echinacea purpurea* extract mildly inhibited the cytochrome P450 isoenzymes CYP1A2, CYP2C19 and CYP3A4, with CYP3A4 being the most affected. However, when this and a number of other products were screened for their ability to inhibit CYP3A4, the inhibitory potencies of the products were found to vary by a factor of 150.[1]

Sometimes, the overall effect of a herbal extract has a different effect on cytochrome P450 than that of an isolated constituent contained in the extract. For example, a mixture

of dietary soya isoflavones containing genistein was found to have no effect on *rat* hepatic CYP1A2 and CYP2E1,[2] whereas isolated genistein was found to inhibit both CYP2E1 and CYP1A2 in experimental studies.[3] Whether this is because of a species difference, a dose-related effect or opposing actions of some constituents within the extract remains to be seen, but it provides another illustration of the dangers of extrapolating results from different types of experiments on individual components to a clinical situation involving a whole mixture.

These brief examples start to illustrate that the mechanisms of drug interactions with herbal medicines bear a great relationship to those of conventional drugs.

1. Modarai M, Gertsch J, Suter A, Heinrich M, Kortenkamp A. Cytochrome P450 inhibitory action of Echinacea preparations differs widely and co-varies with alkylamide content. *J Pharm Pharmacol* (2007) 59, 567–73.
2. Kishida T, Nagamoto M, Ohtsu Y, Watakabe M, Ohshima D, Nashiki K, Mizushige T, Izumi T, Obata A, Ebihara K. Lack of an inducible effect of dietary soy isoflavones on the mRNA abundance of hepatic cytochrome P-450 isozymes in rats. *Biosci Biotechnol Biochem* (2004) 68, 508–15.
3. Helsby NA, Chipman JK, Gescher A, Kerr D. Inhibition of mouse and human CYP 1A- and 2E1-dependent substrate metabolism by the isoflavonoids genistein and equol. *Food Chem Toxicol* (1998) 36, 375–82.

Mechanisms of drug interactions

Some drugs interact together in totally unique ways, but, as the many examples in this publication amply illustrate, there are certain mechanisms of interaction that are encountered time and time again. Some of these common mechanisms are discussed here in greater detail than space will allow in the individual monographs, so that only the briefest reference need be made there. This discussion is restricted to those mechanisms that have been extensively investigated with herbal medicines. Readers interested in a more general discussion of mechanisms are referred to *Stockley's Drug Interactions*.

Very many drugs that interact do so, not by a single mechanism, but often by two or more mechanisms acting in concert, although for clarity most of the mechanisms are dealt with here as though they occur in isolation. For convenience, the mechanisms of interactions can be subdivided into those that involve the pharmacokinetics of a drug, and those that are pharmacodynamic.

Pharmacokinetic interactions

Pharmacokinetic interactions are those that can affect the processes by which drugs are absorbed, distributed, metabolised and excreted (the so-called ADME interactions). Although all these mechanisms are undoubtedly relevant to interactions with herbal medicines, this discussion will mainly focus on cytochrome P450 and drug transporter proteins. Other enzymes have been shown to play a role in the interactions of herbal medicines, such as UDP-glucuronyltransferases (UGTs), but less is known about their effects.

Cytochrome P450 isoenzymes

Although a few drugs are cleared from the body simply by being excreted unchanged in the urine, most are chemically altered within the body to less lipid-soluble compounds, which are more easily excreted by the kidneys. If this were not so, many drugs would persist in the body and continue to exert their effects for a long time. Some drug metabolism goes on in the serum, the kidneys, the skin and the intestines, but the greatest proportion is carried out by enzymes that are found in the liver, mainly cytochrome P450. Cytochrome P450 is not a single entity, but is in fact a very large family of related isoenzymes, about 30 of which have been found in human liver tissue. However, in practice, only a few specific subfamilies seem to be responsible for most (about 90%) of the metabolism of the commonly used drugs. The most important isoenzymes are: CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4. Some of these isoenzymes are also found in the gut wall.

Drugs and herbs affecting or metabolised by the cytochrome P450 isoenzyme CYP1A2†

Inducers	Substrates*	Inhibitors
Cannabis (modest clinical effects with smoking)	Caffeine	Boswellia (*in vitro* effects with gum resin)
Danshen (*in vitro* effects do not appear to be clinically relevant)	Clomipramine	Chamomile, German (moderate effects with tea given to *rats*)
Liquorice (glycyrrhizin constituent studied in *mice*, effects may be weaker clinically)	Clozapine	Dandelion (moderate to potent effects with tea given to *rats*)
St John's wort (*in vitro* induction of only minor clinical relevance)	Duloxetine	Feverfew (*in vitro* evidence only)
	Frovatriptan	Ginkgo (*in vitro* effects do not appear to be clinically relevant)
	Olanzapine	
	Rasagiline	
	Ropinirole	
	Tacrine	
	Theophylline	
	Tizanidine	
	Zolmitriptan	

* shown to be clinically relevant in drug–drug interaction studies

† Note that *in vitro* effects are not necessarily replicated *in vivo*; findings *in vivo* often appear weaker than those *in vitro*. The presence of an *in vitro* effect suggests that clinical study is warranted.

Drugs and herbs affecting or metabolised by the cytochrome P450 isoenzyme CYP3A4†

Inducers	Substrates*	Inhibitors
Echinacea (*in vitro* studies supported by clinical data, but any effect modest. Note inhibition also reported)	**Antiarrhythmics** (Amiodarone, Disopyramide, Lidocaine oral, Propafenone, Quinidine)	Bearberry (*in vitro* evidence only, effects vary greatly between products)
Ginkgo (*in vitro* studies supported by clinical data, but any effect modest. Note inhibition also reported)	**Anticholinesterases, centrally acting** (Donepezil, Galantamine)	Bitter orange (juice known to have clinically relevant effects, supplement has no effects; difference possibly due to constituents)
Liquorice (glycyrrhizin constituent studied in *mice*, effects may be weaker clinically)	**Antihistamines** (Astemizole, Terfenadine)	Black cohosh (effects *in vitro* are probably not clinically relevant)
Rooibos (*in vitro* studies suggest moderate to potent effects)	**Antimigraine drugs** (Eletriptan, Ergot derivatives)	Cat's claw (*in vitro* studies suggest potent effects)
St John's wort (clinically established, potency appears to vary with hyperforin content)	**Antineoplastics** (Busulfan, Cyclophosphamide, Ifosfamide, Imatinib, Irinotecan, Tamoxifen, Taxanes, Teniposide, Toremifene, Vinblastine, Vincristine)	Cranberry (*in vitro* studies suggest modest effects but studies in humans suggest any effect is not clinically relevant)
	Antipsychotics (Pimozide, Quetiapine)	Echinacea (*in vitro* studies supported by clinical data, but any effect modest. Note induction also reported)
	Azoles (Itraconazole, Voriconazole)	Feverfew (*in vitro* evidence only)
	Benzodiazepines and related drugs (Alprazolam, Triazolam, Midazolam; Buspirone, Zolpidem, Zopiclone)	Garlic (effects *in vitro* are probably not clinically relevant)
	Calcium-channel blockers (Diltiazem, Felodipine, Lercanidipine)	Ginkgo (*in vitro* studies supported by clinical data, but any effect modest. Note induction also reported)
	Corticosteroids (Budesonide, Dexamethasone, Fluticasone, Hydrocortisone, Methylprednisolone)	Ginseng (ginsenoside constituents studied; *in vitro* effects are probably not clinically relevant)
	Dopamine agonists (Bromocriptine, Cabergoline)	Goldenseal (*in vitro* studies suggest potent effects, but studies in humans suggest only modest clinical effects)
	Hormones (Hormonal contraceptives, Oestrogens, Progestogens)	Grapefruit (juice has moderate clinical effects; not known if supplements interact similarly)
	Immunosuppressants (Ciclosporin, Sirolimus, Tacrolimus)	Milk thistle (*in vitro* studies supported by some clinical data, but any effect modest)
	Opioids (Alfentanil, Buprenorphine, Fentanyl, Methadone)	Pepper (*in vitro* piperine (a constituent) has some effect, but ethanolic extracts of the fruit had no clinically significant effects)
	Phosphodiesterase type-5 inhibitors (Sildenafil, Tadalafil, Vardenafil)	Resveratrol (*in vitro* studies suggest modest effects)
	Protease inhibitors (Amprenavir, Atazanavir, Darunavir, Fosamprenavir, Indinavir, Nelfinavir, Ritonavir, Saquinavir, Tipranavir)	Rhodiola (*in vitro* effects with a root extract)
	Statins (Atorvastatin, Lovastatin, Simvastatin)	Saw palmetto (effects *in vitro* are not clinically relevant)
	Miscellaneous (Aprepitant, Bosentan, Carbamazepine, Cilostazol, Cisapride, Delavirdine, Dutasteride, Eplerenone, Maraviroc, Reboxetine, Rifabutin, Sibutramine, Solifenacin, Tolterodine)	Turmeric (curcumin constituent studied; *in vitro* effects are potent)

* shown to be clinically relevant in drug–drug interaction studies

† Note that *in vitro* effects are not necessarily replicated *in vivo*; findings *in vivo* often appear weaker than those *in vitro*. The presence of an *in vitro* effect suggests that clinical study is warranted.

(a) Enzyme induction

Some herbal medicines can have a marked effect on the extent of first-pass metabolism of conventional drugs by inducing the cytochrome P450 isoenzymes in the gut wall or in the liver. A number of herbs have been studied specifically for their effects on these isoenzymes. Those that appear to cause clinically relevant induction of specific isoenzymes are grouped in a series of tables, along with the conventional drugs that are substrates for this isoenzyme. See the tables Drugs and herbs affecting or metabolised by the cytochrome P450 isoenzyme CYP1A2, page 7, and Drugs and herbs affecting or metabolised by the cytochrome P450 isoenzyme CYP3A4, page 8.

The extent of the enzyme induction depends on the herbal medicine, its dosage, and even the specific extract used (see Variability of herbal medicines, page 6). It may take days or even 2 to 3 weeks to develop fully, and may persist for a similar length of time when the enzyme inducer is stopped. This means that enzyme induction interactions can be delayed in onset and slow to resolve. These effects have been seen with St John's wort, page 362.

If one drug reduces the effects of another by enzyme induction, it may be possible to accommodate the interaction simply by raising the dosage of the drug affected, but this requires good monitoring, and there are obvious hazards if the inducing drug is eventually stopped without remembering to reduce the dosage again. The raised drug dosage may be an overdose when the drug metabolism has returned to normal. This strategy is more complicated with herbal medicines; the intake of a set amount of the herbal medicine would need to be maintained for this approach to work, and this is difficult because the interacting constituent may vary between products, and even between different batches of the same product.

(b) Enzyme inhibition

More common than enzyme induction is the inhibition of enzymes. This results in the reduced metabolism of an affected drug, so that it may begin to accumulate within the body, the effect usually being essentially the same as when the dosage is increased. Unlike enzyme induction, which may take several days or even weeks to develop fully, enzyme inhibition can occur within 2 to 3 days, resulting in the rapid development of toxicity. An example is the effect of grapefruit and grapefruit juice, which seem to inhibit the cytochrome P450 isoenzyme CYP3A4, mainly in the gut, and therefore reduce the metabolism of oral calcium-channel blockers. See Grapefruit + Calcium-channel blockers, page 237.

A number of herbs have been studied specifically for their effects on cytochrome P450 isoenzymes. Those that appear to have clinically relevant effects on specific isoenzymes are grouped in a series of tables, along with the conventional drugs that are substrates for this isoenzyme. See the tables Drugs and herbs affecting or metabolised by the cytochrome P450 isoenzyme CYP1A2, page 7, and Drugs and herbs affecting or metabolised by the cytochrome P450 isoenzyme CYP3A4, page 8.

The clinical significance of many enzyme inhibition interactions depends on the extent to which the serum levels of the drug rise. If the serum levels remain within the therapeutic range the interaction may not be clinically important.

(c) Predicting interactions involving cytochrome P450

It is interesting to know which particular isoenzyme is responsible for the metabolism of drugs because by doing *in vitro* tests with human liver enzymes it is often possible to explain why and how some drugs interact. For example, ciclosporin is metabolised by CYP3A4, and we know that St John's wort is a potent inducer of this isoenzyme, so that it comes as no surprise that St John's wort, page 368, reduces the effects of ciclosporin.

What is very much more important than retrospectively finding out why drugs and herbal medicines interact is the knowledge that such *in vitro* tests can provide about forecasting which other drugs may possibly also interact. This may reduce the numbers of expensive clinical studies in subjects and patients and avoids waiting until significant drug interactions are observed in clinical use. A lot of effort is being put into this area of drug development, and it is particularly important for herbal medicines, where it seems unlikely that expensive clinical studies will be routinely conducted. However, at present such prediction is not always accurate because all of the many variables that can come into play are not known (such as how much of the enzyme is available, the concentration of the drug at the site of metabolism and the affinity of the drug for the enzyme). Remember too that some drugs can be metabolised by more than one cytochrome P450 isoenzyme (meaning that this other isoenzyme may be able to 'pick up' more metabolism to compensate for the inhibited pathway), some drugs (and their metabolites) can both induce a particular isoenzyme and be metabolised by it, and some drugs (or their metabolites) can inhibit a particular isoenzyme but not be metabolised by it. With so many factors possibly impinging on the outcome of giving two or more drugs together, it is very easy to lose sight of one of the factors (or not even know about it) so that the sum of 2 plus 2 may not turn out to be the 4 that you have predicted.

Drug transporter proteins

Drugs and endogenous substances are known to cross biological membranes, not just by passive diffusion, but also by carrier-mediated processes, often known as transporters. Significant advances in the identification of various transporters have been made, although the contribution of many of these to drug interactions in particular, is still being investigated. The most well-known drug transporter protein is P-glycoprotein.

More and more evidence is accumulating to show that some drug interactions occur because they interfere with the activity of P-glycoprotein. This is an efflux pump found in the membranes of certain cells, which can push metabolites and drugs out of the cells and have an impact on the extent of drug absorption (via the intestine), distribution (to the brain, testis or placenta) and elimination (in the urine and bile). So, for example, the P-glycoprotein in the cells of the gut lining can eject some already-absorbed drug molecules back into the intestine resulting in a reduction in the total amount of drug absorbed. In this way P-glycoprotein acts as a barrier to absorption. The activity of P-glycoprotein in the endothelial

cells of the blood–brain barrier can also eject certain drugs from the brain, limiting CNS penetration and effects.

The pumping actions of P-glycoprotein can be experimentally induced or inhibited by some herbal medicines. So for example, the induction (or stimulation) of the activity of P-glycoprotein by capsicum, within the lining cells of the gut, causes digoxin to be ejected into the gut more vigorously. This may result in a fall in the plasma levels of digoxin. See Capsicum + Digoxin, page 116. In contrast, some extracts of danshen appear to inhibit the activity of P-glycoprotein, and may therefore increase digoxin levels. See Danshen + Digoxin, page 162.

There is an overlap between CYP3A4 and P-glycoprotein inhibitors, inducers and substrates. Digoxin is an example of one of the few drugs that is a substrate for P-glycoprotein but not CYP3A4. It is for this reason that it is used as a probe substrate for P-glycoprotein activity, and the effects of herbal medicines on this particular drug have been studied.

Other transporters that are involved in some drug interactions are the organic anion transporters (OATs), organic anion-transporting polypeptides (OATPs) and organic cation transporters (OCTs), which are members of the solute carrier superfamily (SLC) of transporters. The best known example of an OAT inhibitor is probenecid, which affects the renal excretion of a number of drugs. However, the effects of many herbal medicines and drugs on these transporters are less well understood than those of P-glycoprotein, and thus, the role of OATs, OATPs and OCTs in drug interactions is still being elucidated.

Pharmacodynamic interactions

Pharmacodynamic interactions are those where the effects of one drug are changed by the presence of another drug at its site of action. Sometimes the drugs directly compete for particular receptors but often the reaction is more indirect and involves interference with physiological mechanisms. These interactions are much less easy to classify neatly than those of a pharmacokinetic type.

(a) Additive or synergistic interactions

If two drugs that have the same pharmacological effect are given together the effects can be additive. For example, alcohol depresses the CNS and, if taken in moderate amounts with normal therapeutic doses of herbal medicines (e.g. valerian), may increase drowsiness. See Valerian + Alcohol, page 397.

Sometimes the additive effects are solely toxic (e.g. theoretical additive nephrotoxicity, see Ginkgo + Aminoglycosides, page 209). It is common to use the terms ‘additive’, ‘summation’, ‘synergy’ or ‘potentiation’ to describe what happens if two or more drugs behave like this. These words have precise pharmacological definitions but they are often used rather loosely as synonyms because in practice it is often very difficult to know the extent of the increased activity, that is to say whether the effects are greater or smaller than the sum of the individual effects.

One particular additive effect is well known to occur between the herbal medicine St John’s wort, page 362, and conventional medicines. This is serotonin syndrome. The reasons for this effect are not fully understood, but the serotonin syndrome is thought to occur as a result of over-stimulation of the 5-HT_{1A} and 5-HT_{2A} receptors and possibly other serotonin receptors in the CNS (in the brain stem and spinal cord in particular) due to the combined effects of two medicines (herbal or conventional). Serotonin syndrome can occur exceptionally after taking only one substance that causes over-stimulation of these 5-HT receptors, but much more usually it develops when two or more drugs (so-called serotonergic or serotomimetic drugs) act in concert. The characteristic symptoms fall into three main areas, namely altered mental status (agitation, confusion, mania), autonomic dysfunction (diaphoresis, diarrhoea, fever, shivering) and neuromuscular abnormalities (hyperreflexia, incoordination, myoclonus, tremor).

The syndrome can develop shortly after one serotonergic drug is added to another, or even if one is replaced by another without allowing a long enough washout period in between, and the problem usually resolves within about 24 hours if both drugs are withdrawn and supportive measures given. Non-specific serotonin antagonists (cyproheptadine, chlorpromazine, methysergide) have also been used for treatment. Most patients recover uneventfully, but there have been a few fatalities.

It is still not at all clear why many patients can take two, or sometimes several, serotonergic drugs together without problems, while a very small number develop this serious toxic reaction, but it certainly suggests that there are other factors involved that have yet to be identified. The full story is likely to be much more complex than just the simple additive effects of two drugs.

(b) Antagonistic or opposing interactions

In contrast to additive interactions, there are some pairs of drugs with activities that are opposed to one another. For example, the coumarins can prolong the blood clotting time by competitively inhibiting the effects of dietary vitamin K. If the intake of vitamin K is increased, the effects of the oral anticoagulant are opposed and the prothrombin time can return to normal, thereby cancelling out the therapeutic benefits of anticoagulant treatment. It has been proposed that the vitamin K content of herbal medicines may be sufficient to provoke this interaction, but in most cases of normal intake of the herb, this seems unlikely. See Alfalfa + Warfarin and related drugs, page 23, for further discussion of this potential interaction.

Drawing your own conclusions

The human population is a total mixture, unlike selected batches of laboratory animals (same age, weight, sex, strain, etc.). For this reason human beings do not respond uniformly to one or more drugs or even herbal medicines. Our genetic make-up, ethnic background, sex, renal and hepatic functions, diseases and nutritional states, ages and other factors (the route of administration, for example) all contribute towards the heterogeneity of our responses. This means that the outcome of giving one or more drugs to any individual for the first time is never totally predictable because it is a new and unique ‘experiment’. Even so, some idea of the probable outcome of using a drug or a pair of drugs can be based on what has been seen in other patients: the more extensive the data, the firmer the predictions.

The most difficult decisions concern isolated cases of

interaction, many of which achieved prominence only because they were serious. Do you ignore them as 'idiosyncratic' or do you, from that moment onwards, advise against the use of the herbal medicine and conventional drug totally?

There is no simple yes or no answer to these questions, especially as evidence regarding interactions between herbal medicines is often only of an experimental nature. The delicate balance between whether or not to give the drug has then to be set against the actual severity of the reaction reported and weighed up against how essential it is to use the combination in question.

When deciding the possible first-time use of any two drugs in any particular patient, you need to put what is currently known about these drugs against the particular profile of your patient. Read the monograph. Consider the facts and conclusions, and then set the whole against the backdrop of your patient's unique condition (age, disease, general condition, and so forth) so that what you eventually decide to do is well thought out and soundly based. We do not usually have the luxury of knowing absolutely all the facts, so that an initial conservative approach is often the safest.

It is now quite impossible to remember all the known clinically important interactions and how they occur but there are some broad general principles that are worth remembering:

- Be on the alert with any drugs that have a narrow therapeutic window or where it is necessary to keep serum levels at or above a suitable level (e.g. anticoagulants, antidiabetic drugs, antiepileptics, antihypertensives, anti-infectives, antineoplastic cytotoxics, digitalis glycosides, immunosuppressants, etc.).
- Think about the basic pharmacology of the drugs under consideration so that obvious problems (additive CNS depression, for example) are not overlooked, and try to think what might happen if drugs that affect the same receptors are used together. And don't forget that many drugs affect more than one type of receptor.
- Keep in mind that the elderly are at risk because of reduced liver and renal function on which drug clearance depends.

Acidophilus

Lactobacillus acidophilus (Lactobacillaceae)

Use and indications

Lactobacillus acidophilus are lactic-acid producing bacterial organisms that are normally present in the human gut. Acidophilus supplements are primarily taken as a probiotic, to restore or maintain healthy microbial flora. Acidophilus has also been used to treat diarrhoea, irritable bowel syndrome, lactose intolerance, urinary tract infections and yeast-based infections (such as those caused by *Candida albicans*), and for general digestive problems. It is available in various forms ranging from capsules to yoghurts.

Pharmacokinetics

No relevant pharmacokinetic data found.

Interactions overview

Acidophilus is a bacterial organism, and therefore it may lead to systemic infection in immunosuppressed patients, although this effect is expected to be rare. Antibacterials and drugs that are dependent on bacterial degradation to release active constituents, namely sulfasalazine, may also be expected to interact.

A

Acidophilus + Antibacterials

The interaction between acidophilus and antibacterials is based on experimental evidence only.

Clinical evidence

No interactions found.

Experimental evidence

Lactobacillus acidophilus are Gram-positive, facultative anaerobic bacteria and as such can be inhibited or killed by antibacterials that are effective against this type of bacteria. **Ampicillin**,[1–3] **ampicillin** with **sulbactam**,[3] **benzylpenicillin**,[2,3] **cefalotin**,[1] **chloramphenicol**,[2,3] **clindamycin**,[1,3,4] **erythromycin**,[2,3] **gentamicin**,[3] **linezolid**,[3] **oxytetracycline**,[3] **penicillin**,[1] **quinupristin/dalfopristin**,[3] **streptomycin**,[3] **tetracycline**[2] and **vancomycin**[3] have been found to inhibit acidophilus populations.

Mechanism

Antibacterials kill or inhibit the growth of bacterial populations through various different mechanisms.

Importance and management

Depending on the particular strain of acidophilus and the antibacterial dose, the desired therapeutic effect of acidophilus may be significantly reduced or even abolished by these antibacterials.

1. Bayer AS, Chow AW, Concepcion N, Guze LB. Susceptibility of 40 lactobacilli to six antimicrobial agents with broad gram-positive anaerobic spectra. *Antimicrob Agents Chemother* (1978) 14, 720–2.
2. Hummel AS, Hertel C, Holzapfel WH, Franz CMAP. Antibiotic resistances of starter and probiotic strains of lactic acid bacteria. *Appl Environ Microbiol* (2007) 73, 730–9.
3. Klare I, Konstabel C, Werner G, Huys G, Vankerckhoven V, Kahlmeter G, Hildebrandt B, Müller-Bertling S, Witte W, Goossens H. Antimicrobial susceptibilities of *Lactobacillus*, *Pediococcus* and *Lactococcus* human isolates and cultures intended for probiotic or nutritional use. *J Antimicrob Chemother* (2007) 59, 900–12.
4. Lidbeck A, Edlund C, Gustafsson JÅ, Kager L, Nord CE. Impact of *Lactobacillus acidophilus* administration on the intestinal microflora after clindamycin treatment. *J Chemother* (2005) 1, 630–2.

Acidophilus + Food

No interactions found. Acidophilus is often present in live yoghurt.

Acidophilus + Herbal medicines; Soya isoflavones

Acidophilus does not generally affect the metabolism of soya isoflavones.

Clinical evidence

In a randomised study 20 women who had been successfully treated for breast cancer and 20 women without a history of cancer were given a soya protein isolate containing 640 micrograms/kg of isoflavones daily (34% daidzein, 57% genistein and 9% glycitein), with three probiotic capsules (*DDS Plus*), containing *Lactobacillus acidophilus* and ***Bifidobacterium longum***, daily for 42 days. In general, the probiotics did not affect the plasma isoflavone concentrations, although two of the subjects had altered plasma concentrations of equol, a daidzein metabolite. No adverse effects were reported in the study.[1] In another study, the same probiotic did not alter the cholesterol-lowering effects of the isoflavones.[2]

Experimental evidence

No relevant data found.

Mechanism

The gut bacterial flora metabolises daidzein to equol, which is thought to be responsible for reduced breast cancer risk. The authors hypothesised that increasing the populations of bacteria, by using probiotics, levels of equol would increase.

Importance and management

Increasing the populations of bacteria in the gut does not appear to have a significant effect on the metabolism of soya isoflavones. Note that the metabolism of isoflavones is variable, due to differences in gut flora between individuals, and so the effects of any interaction between acidophilus and isoflavones are likely to differ between individuals. For more information on the interactions of isoflavones in general, see under isoflavones, page 258.

1. Nettleton JA, Greany KA, Thomas W, Wangen KE, Adlercreutz H, Kurzer MS. Plasma phytoestrogens are not altered by probiotic consumption in postmenopausal women with and without a history of breast cancer. *J Nutr* (2004) 134, 1998–2003.
2. Greany KA, Nettleton JA, Wangen KE, Thomas W, Kurzer MS. Probiotic consumption does not enhance the cholesterol-lowering effect of soy in postmenopausal women. *J Nutr* (2004) 134, 3277–83.

Acidophilus + Immunosuppressants

An isolated case report describes fatal septicaemia in an immunosuppressed woman taking cyclophosphamide and fludrocortisone who ate live yoghurt containing *Lactobacillus rhamnosus*, which is closely related to acidophilus.

Clinical evidence

A 42-year-old woman taking **cyclophosphamide** and **fludrocortisone** for Sjögren's syndrome developed pneumonia and secondary ***Lactobacillus rhamnosus*** septicaemia, which proved to be fatal, after taking a short course of supermarket own-brand live yoghurt for diarrhoea.[1] Note that ***Lactobacillus rhamnosus*** is a species closely related to *Lactobacillus acidophilus*.

Experimental evidence

No relevant data found.

Mechanism

The immunosuppressed nature of the patient is thought to have provided a more conducive environment for the introduced bacteria to establish a sufficient population to reach a pathogenic threshold.

Importance and management

Although not a drug interaction in the strictest sense, it would be sensible to assume that introducing bacteria in the form of a probiotic to an immunosuppressed patient should be undertaken with great care or perhaps avoided: note that patients who have undergone a transplantation and who are immunosuppressed are often advised to avoid foods such as live yoghurts.

Remember that, as immunosuppression secondary to corticosteroid use is dependent on numerous factors related to the dosage and duration of intake, not all patients taking corticosteroids are likely to be immunosuppressed and therefore they will not necessarily need to avoid acidophilus-containing products.

1. MacGregor G, Smith AJ, Thakker B, Kinsella J. Yoghurt biotherapy: contraindicated in immunosuppressed patients? *Postgrad Med J* (2002) 78, 366–7.

Acidophilus + Sulfasalazine

The interaction between acidophilus and sulfasalazine is based on experimental evidence only.

Clinical evidence

No interactions found.

Experimental evidence

In an experimental study about 85 to 95% of a dose of sulfasalazine was broken down by several different strains of *Lactobacillus acidophilus*.[1]

Mechanism

The azo link of sulfasalazine is split by anaerobic bacteria in the colon to release sulfapyridine and 5-aminosalicylic acid, the latter being the active metabolite that acts locally in the treatment of inflammatory bowel disease. The lipophilic nature of sulfasalazine is thought to enable it to reach the site of azoreductase activity within the bacterial cell by passive diffusion across the cell membrane.

Importance and management

Sulfasalazine is generally thought to be 'activated' by its metabolism to release 5-aminosalicylic acid by bacteria in the colon. By introducing more bacteria, the metabolism could be increased. However, metabolism may also occur earlier, in the small intestine, which could be detrimental as one metabolite, sulfapyridine, is rapidly absorbed from the small intestine and can contribute to renal toxicity.

It should be noted, however, that this is a rather old experimental study that appears to be the only one of its kind in the literature. Also, the pH of the gut is much lower than the pH used in the experimental study and there is a degree of interindividual variability in populations of bacterial flora. Taking all this into account, this interaction seems unlikely to be clinically relevant.

1. Pradhan A, Majumdar MK. Metabolism of some drugs by intestinal lactobacilli and their toxicological considerations. *Acta Pharmacol Toxicol (Copenh)* (1986) 58, 11–15.

Agnus castus

Vitex agnus-castus L. (Lamiaceae)

Synonym(s) and related species

Agni casti, Chasteberry, Chaste tree, Monk's pepper.

Pharmacopoeias

Agnus Castus (*BP 2009*, *Ph Eur 6.4*); Chaste Tree (*USP 32*).

Constituents

Agnus castus is usually standardised to the content of the **flavonoid casticin** (dried ripe fruit and powdered extracts contain a minimum of 0.08%, *USP 32*), and sometimes also the iridoid glycoside **agnuside** (dried ripe fruit and powdered extracts contain a minimum of 0.05%, *USP 32*). Other major constituents are the **labdane** and **clerodane diterpenes** (including rotundifuran, 6β,7β-diacetoxy-13-hydroxy-labda-8,14-diene, vitexilactone). Other **flavonoids** include orientin, apigenin and penduletin.

Use and indications

Traditional use of the dried ripe fruit of agnus castus focuses on menstrual disorders in women resulting from corpus luteum deficiency, such as amenorrhoea, metrorrhagia and symptoms of premenstrual syndrome, including mastalgia. It has also been used to alleviate some menopausal symptoms and to promote lactation. In men it has been used to suppress libido and treat acne.

Pharmacokinetics

No relevant pharmacokinetic data for agnus castus found. For information on the pharmacokinetics of individual flavonoids present in agnus castus, see under flavonoids, page 186.

Interactions overview

A comprehensive systematic review of data from spontaneous adverse event reporting schemes and published clinical studies, post-marketing surveillance studies, surveys and case reports was carried out in September 2004 to investigate the safety of agnus castus extracts. No drug interactions were identified.[1] Agnus castus extracts used in the data reviewed included *Agnolyt*, *Agnucaston*, *Strotan* and *ZE 440*.

However, agnus castus has dopamine agonist properties, and may therefore interact with drugs with either dopamine agonist or dopamine antagonist actions.

Agnus castus contains oestrogenic compounds but it is unclear whether the effects of these compounds are additive, or antagonistic, to oestrogens and oestrogen antagonists (e.g. tamoxifen). Although agnus castus binds with opioid receptors, no serious interaction with opioid analgesics would be expected.

For information on the interactions of flavonoids, see under flavonoids, page 186.

1. Daniele C, Thompson Coon J, Pittler MH, Ernst E. *Vitex agnus castus*: a systematic review of adverse effects. *Drug Safety* (2005) 28, 319–32.