Herbal Medicines

Third edition

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Pharmaceutical Press

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The views expressed in this book are those of the authors and do not represent those of the UK Medicines and Healthcare products Regulatory Agency, European Medicines Agency, World Health Organization, or any other institution or organisation mentioned. Mention of specific product names is for clarity and identification purposes and does not represent endorsement.

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This book is dedicated to the memory of
the late Dr W Gwynne Thomas,
former Director of Pharmaceutical Sciences at the
Royal Pharmaceutical Society of Great Britain.
The inspiration for the book came from him and
it is due to his efforts that the necessary funding
was obtained.

Preface to the Third Edition

This third edition of *Herbal Medicines: A guide for healthcare professionals* comes a little over ten years after publication of the first edition, and reflects continuing public, professional, research, commercial and other interests in medicinal plants. At the same time, there have been ongoing concerns surrounding the quality, safety and efficacy of herbal medicinal products, and heightened awareness of the need to protect the public against poor-quality and unsafe products. Pharmacists, doctors, nurses, herbal-medicine practitioners and other healthcare providers should be knowledgeable about these issues and should be able to advise patients and the public on the safe, effective and appropriate use of herbal preparations; this book aims to provide pharmacists and other healthcare professionals with summarised, yet sufficiently detailed, scientific information to enable them to do so.

Herbal medicines continue to be a popular healthcare choice with the general public not only for health maintenance and well-being, minor ailments (e.g. coughs and colds), chronic conditions (e.g. back pain) and serious chronic diseases (e.g. asthma, cancer, depression, diabetes), but also for 'enhancement' of functions or processes, such as the use of *Ginkgo biloba* products for memory enhancement. The general public receives information on herbal medicines through various sources, including popular magazines and newspaper articles, as well as television, internet and other sources of advertising literature provided by manufacturers. Much of this information is presented uncritically, and targeted to the consumer along with details of substantial price reductions on products, including continuous sales promotions, that often are the main recommendations for the products. There is an increasing number of products that respond to the public demand for so-called 'lifestyle' medicines, and manufacturers market, for example, herbal alternatives to Viagra (sildenafil), 'slimming/weight-loss' preparations, 'hangover' cures, and breast-enlargement products. Typically, these types of products are sold over the internet without any assurance of their quality, safety and efficacy.

The last decade has seen several important developments with respect to herbal medicines. The most significant of these has been the introduction of a new regulatory framework for traditional herbal medicines in the UK and the 27 other member states of the European Union (EU) following the implementation in 2005 of the EU Directive on Traditional Herbal Medicinal Products. Several other countries worldwide have introduced new legislation to regulate herbal medicinal products: Australia and Canada, for example, have been particularly active in this respect. That the regulatory landscape for herbal medicines has changed substantially has required a full revision of the 'Introduction to the Monographs', which in this edition can be found under 'How to Use *Herbal Medicines*'; this now includes details of new legislation in Europe and a summary of regulations for herbal medicines in several other countries.

Although there are new regulations, in Europe there is a transitional period until 2011 to allow manufacturers time to comply with the new requirements, so issues relating to the quality, safety and efficacy of herbal medicines are likely to continue, even beyond the next edition of this book! Therefore, with respect to quality, consumers and healthcare professionals should be aware that the labels of unlicensed (unregulated) herbal medicines may not reflect their actual contents, and that the precise constituents of herbal medicines containing the same herbal ingredient(s) but produced by different manufacturers are likely to differ. The quality of herbal medicines (i.e. uniformity of dose) is important for their efficacy: clinical trial results for a particular herbal medicinal product cannot necessarily be extrapolated to other products containing the same ingredient, since their precise contents may differ. Details of herbal medicinal products tested in clinical trials are provided in individual monographs in this book. There is an increasing amount of research comprising qualitative (i.e. the profile of chemical constituents) and quantitative (quantity of chemical constituents) analysis of herbal medicines and showing variations in the contents of different manufacturers' products. For those herbal ingredients for which there is substantial information, and for commonly encountered herbal ingredients, we have summarised the findings of these analyses in a new section in some monographs on *Quality of plant material and commercial products* (for examples, see the monographs on St John's wort and Echinacea).

The quality of herbal medicines is also important as regards their safety, and safety concerns with herbal medicines, including intrinsic toxicity as well as problems due to adulteration and contamination, continue to arise. This edition includes new monographs on kava (*Piper methysticum*) and greater celandine (*Chelidonium majus*) and a fully revised monograph on black cohosh (*Cimicifuga racemosa*), all of which have been associated with hepatotoxic reactions. The concurrent use of herbal and other medicines remains a major concern for healthcare professionals because of the potential for important drug interactions. Evidence of pharmacokinetic and pharmacodynamic interactions between St John's wort (*Hypericum perforatum*) and 'conventional' medicines emerged in the year 2000 and, since then, reports have been made of interactions between other herbal medicines and conventional medicines, typically those with a low therapeutic index. At present though, there has been little formal clinical research into interactions between herbal and other medicines, and information relies mainly on spontaneous reports and, to some extent, findings of *in-vitro* studies of the effects of certain herbal medicines on cytochrome P450 drug-metabolising enzymes. Information on known and potential interactions is summarised in the Appendices to this book, and further information and detail is provided in the individual monographs.

Continual vigilance and reporting of adverse effects, including interactions and problems related to poor quality, associated with herbal medicines is essential in order to detect safety issues as soon as possible. In the UK, pharmacists and other state-registered healthcare providers and, since 2005, patients and consumers, can report suspected adverse drug reactions (ADRs) associated with herbal medicines directly to the Medicines and Healthcare products Regulatory Agency (MHRA) using 'yellow card' report forms. These forms are included in the *British National Formulary* and available on-line (*see* www.mhra.gov.uk), and for the first time several are included in this book so that they may be more readily at hand to healthcare professionals using this book for information on adverse effects experienced and reported

to them by consumers and patients. Many other countries have an ADR reporting scheme similar to that of the UK and encourage reporting of suspected herbal ADRs, at least by healthcare professionals. The World Health Organization's Uppsala Monitoring Centre in Sweden receives such reports from over 70 countries, including Australia, Canada, France, Germany, New Zealand, UK and the USA, and we have summarised this information for a number of herbal medicines for which there have been important safety concerns (see individual monographs).

The effects of herbal medicines are, of course, brought about by their chemical constituents. It may not be fully recognised by some individuals that while, for example, aspirin tablets contain a measured quantity (within narrow limits) of a single active chemical compound, tablets (and indeed other dosage forms) of a herbal medicine typically contain a complex mixture of many (hundreds or more) chemical compounds. In order to appreciate the quality control and quality assurance procedures that are essential for herbal medicinal products and to understand their pharmacological and toxicological effects, it is necessary to be aware of the different types of chemical constituents, e.g. alkaloids, glycosides, flavonoids, etc, that may be present, as well as the individual constituents in specific herbal medicines. This edition includes two new features which provide this information: chemical structural formulae are included with virtually every monograph to supplement the textual information on constituents, and a new chapter 'Chemical Constituents of Plants Used as Herbal Medicines' has been added, which summarises the different groups of natural product compounds (e.g. alkaloids, glycosides, flavonoids, terpenes) that are present in medicinal plants.

The first edition of this book provided information on herbal medicines available in pharmacies in the UK, whereas we have expanded the scope of this third edition to include new monographs on herbal medicines that may not necessarily be found in UK pharmacies but which are of public or professional interest. Hence, this edition includes new monographs on butterbur (*Petasites hybridus*), greater celandine (*Chelidonium majus*), kava (*Piper methysticum*) and rhodiola (*Rhodiola rosea*). Kava has been prohibited in the UK since 2002 because of its association with hepatotoxic reactions; we include a monograph here as it is possible that consumers and patients in the UK may obtain supplies from overseas. At least 10 existing monographs on popular herbal medicines have been completely revised, substantial updates and revisions have been made to over 20 other monographs, and minor amendments have been made to all remaining monographs. In addition, in response to comments from practising pharmacists, academics and other users of this book, this edition includes photographs of the crude herbal drugs which feature in the monographs as well as, for many monographs, the plants from which they originate. Also for the first time the individual monographs contain information from several countries on marketed products containing the respective herbal ingredients. We hope that these new features will be both useful and pleasing to the eye! As always, keeping a book up to date is a never-ending task, and the explosion in the scientific literature on herbal medicines makes this ever more difficult. In the last five years, there have been over 500 scientific papers published on St John's wort alone, and it is impossible and undesirable to describe each of them. The need for a book that reviews and summarises all this information has, perhaps, never been greater and we hope that this edition will provide healthcare professionals with the information they need to be able to advise their patients, competently and confidently, on the safe, effective and appropriate use of herbal medicines.

Constructive criticism of the contents of *Herbal Medicines* is welcome and may be used to assist in the preparation of any future editions. The reader is asked to send any comments to the publisher by post or email (pharmpress@rpsgb.org).

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Most of the herbal plant photographs were taken in major European botanical gardens. Photographs of the drug material were taken from materials supplied by reputable German herbal medicinal product suppliers.

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About the Authors

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Joanne Barnes obtained a degree in Pharmacy from the University of Nottingham in 1988, a postgraduate Certificate in Pharmacovigilance and Pharmacoepidemiology from the London School of Hygiene and Tropical Medicine in 1999, and a PhD in Pharmacy from the School of Pharmacy, University of London in 2001. She has been registered as a pharmacist with the Royal Pharmaceutical Society of Great Britain since 1989, was made a Fellow of the Linnean Society of London in 2003 and achieved registration as a pharmacist in New Zealand in 2007. She was Research Fellow in Complementary Medicines in the Department of Complementary Medicine, University of Exeter (1996–1999), Research Fellow (1999–2002) and Lecturer in Phytopharmacy (2002–2005) in the Centre for Pharmacognosy and Phytotherapy, School of Pharmacy, University of London, UK and, since 2005, has been Associate Professor in Herbal Medicines, School of Pharmacy, Faculty of Medical and Health Sciences, University of Auckland, New Zealand. Her research focuses on the utilisation, efficacy and safety of herbal medicines, particularly in exploring issues related to pharmacovigilance. Before embarking on an academic career, she practised as a hospital clinical pharmacist, as a medical information pharmacist in the pharmaceutical industry and worked in pharmaceutical publishing.

She was Editor (1996–1999) and a co-founder of the journal *Focus on Alternative and Complementary Therapies* (FACT), Co-editor (2003–2005) of *Complementary Therapies in Medicine* and is an Associate Editor of *Phytochemistry Letters* and a member of the editorial boards of *Phytotherapy Research*, *Drug Safety* and the *International Journal of Pharmacy Practice*. She is a member of the Health Canada Natural Health Product Directorate's Expert Resource Group, the RPSGB's complementary medicine working group, and was a member of the UK Medicines and Healthcare products Regulatory Agency's Independent Review Panel for the Classification of Borderline Products (2000–2005).

Dr Linda A Anderson

BPharm, PhD, FRPharmS

Linda Anderson obtained her first degree in Pharmacy and her PhD in Pharmacognosy at the Welsh School of Pharmacy in Cardiff. She was a postdoctoral research and teaching fellow at the School of Pharmacy, University of London from 1981 to 1987.

Dr Anderson joined the Medicines and Healthcare products Regulatory Agency (MHRA, Department of Health, UK; formerly Medicines Control Agency) in 1987.

Within the MHRA, she was initially involved in the assessment of new chemical entities and is now mainly involved with abridged applications and has specific responsibility for herbal products. She is Principal Assessor to the Committee on Safety of Medicine's (CSM) Expert Advisory Group on Chemistry, Pharmacy and Standards (CPS) and is UK delegate to the European Committee on Human Medicinal Products (CHMP) Quality Working Party. Dr Anderson is also UK Delegate to the European Medicines Agency (EMEA) Committee on Herbal Medicinal Products (HMPC), a member of the Herbal Medicines Advisory Committee (HMAC) of the MHRA, and is Vice-Chair of the British Pharmacopoeia Expert Advisory Group on Herbals and Complementary Medicines. She is a member of the Royal Pharmaceutical Society's Science Committee's working group on complementary/alternative medicine.

Linda Anderson has been awarded a Fellowship of the Royal Pharmaceutical Society of Great Britain (2001).

Professor J David Phillipson

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David Phillipson graduated BSc in Pharmacy (1956), MSc (1959), and DSc (1979) from the University of Manchester, and PhD (1965) from the University of London. He was Lecturer in Pharmacognosy (1961–1972) at the Department of Pharmacy, Chelsea College, London, and Senior Lecturer (1973–1979), Reader in Phytochemistry (1979–1981), and Professor and Head of the Department of Pharmacognosy (1981–1994) at the School of Pharmacy, University of London. On retirement he became Emeritus Professor of Pharmacognosy. In 1995 he was appointed as Wilson T S Wang Distinguished International Visiting Professor at the Chinese University of Hong Kong from January to June. His research included investigations of the chemistry and biological activities of natural products from higher plants with special interests in indole and isoquinoline alkaloids, and plants used in traditional medicines for the treatment of malaria and other protozoal diseases. Collaboration with the pharmaceutical industry included the application of radioligand–receptor binding assays in the search for natural products with activity in the central nervous system.

David Phillipson has received awards from the Phytochemical Society of Europe including the Tate and Lyle Award (1982), Medal (1994), and the Pergamon Prize for Creativity in Plant Biochemistry (1996). He was awarded the Korber Foundation Prize for Achievement in European Science (1989) in collaboration with Professor MH Zenk of the University of Munich and four other European colleagues, was presented with the Harrison Memorial Medal of the Royal Pharmaceutical Society of Great Britain (1999), and with the Sir Hans Sloane Medal of the Faculty of the History and Philosophy of Medicine and Pharmacy, Society of Apothecaries (2001). In 1985 he was Science Chairman of the British Pharmaceutical Conference and has been Secretary (1977–1982), Vice-Chairman (1982–1984, 1986–1988) and Chairman (1984–1986) of the Phytochemical Society of Europe. He has been awarded Fellowships of the Royal Pharmaceutical Society of Great Britain (1980) and of the School of Pharmacy, University of London (1998).

He has supervised 33 PhD students and 11 postdoctoral researchers, publishing some 222 full research papers, 150 short communications, 42 review articles, and has edited six books on natural products. Collaborative research was established with scientists in many countries world-wide and in 1989 he was appointed Honorary Professor of the Chinese Academy of Medical Sciences at the Institute of Medicinal Plant Research and Development, Beijing, China. For 19 years he was a member of the Natural Products Group of the International Foundation for Science, Sweden, helping to award research grants to individual young scientists in developing countries. He has been a member of a number of national and international committees, including the Herbal Medicines Advisory Committee (HMAC) of the MHRA.

How to Use *Herbal Medicines*

Purpose and Scope

Herbal Medicines is intended to serve as a reference work for pharmacists, doctors, nurses and other healthcare professionals, assisting in their provision of advice on the use of herbal medicines to members of the public. *Herbal Medicines* is not intended to represent a guide to self-diagnosis and self-treatment with herbal medicines, and should not be used as such.

The term 'herbal medicine' or 'herbal medicinal product' (or, less frequently, 'herbal remedy') is used to describe a marketed product, whereas 'herbal ingredient' refers to an individual herb that is present in a herbal medicine. 'Herbal constituent' is used to describe a specific chemical constituent of a herbal ingredient. Thus, as examples, Valerian Tablets are a herbal product, valerian root is a herbal ingredient, and valtrate is a herbal constituent of valerian.

The main criterion for inclusion of a herbal ingredient in the text is its presence in herbal medicines that are used in the UK, particularly those which are sold through pharmacies. In addition, herbs that have recently been the subject of media or scientific interest have been included. The aim of *Herbal Medicines* is to draw the attention of the reader to the reputed actions and uses of herbal ingredients, and to whether or not these have been substantiated by evidence from preclinical and/or clinical studies. In addition, any known or potential toxicities of herbal ingredients, and how these may influence the suitability for inclusion in herbal medicines or for use with conventional medicines, are also discussed.

Introduction to the Monographs

The introductory section to the 152 monographs on the individual herbal ingredients contained in *Herbal Medicines* discusses the legal aspects of herbal medicines including licensed medicines and non-licensed products in the UK and within the European Union (EU). All medicines are assessed for their quality, safety and efficacy and, in the context of herbal medicines, there are often specific criteria which are not encountered in the assessment of other medicines. As a first line in ensuring the safety and efficacy of herbal medicines there is a series of guidelines for quality assessment and this is briefly discussed. In terms of safety, it is a popular conception that because herbs are 'natural' then they must also be safe. This is a misconception, and it is emphasised that some herbal ingredients have the capability to cause adverse effects, whilst some are decidedly toxic. Within the context of the 152 monographs on herbal ingredients, most have documented adverse effects, or the potential to interact with other medication, and few can be recommended for use during pregnancy.

Tables in the Introduction and appendices at the end of the monographs summarise the safety aspects of these herbal ingredients and give information on biologically active herbal ingredients and their active principles. Clinical efficacy has not been established for the majority of the herbal ingredients described in this handbook and, in some instances, there is a lack of documentation for chemical constituents and for pharmacological actions.

The Herbal Monographs

Some 152 monographs on individual herbal ingredients found in herbal products are included, the title used for the monograph being their preferred common name. A data sheet-type format was chosen for the monographs because it was felt important to arrange the relevant information in a format familiar to pharmacists, doctors, nurses and other healthcare professionals. Although conventional data sheets are written for products, it was decided to draw up the data sheets for herbal ingredients and not for specific products, although where possible details are provided of the specific products assessed in the studies discussed.

The headings used in the herbal monographs are listed below with a brief explanation of the information provided under them.

Monograph title	Common name for the herbal ingredient; if more than one common name exists, this is the chosen preferred name.
Summary and Pharmaceutical Comment	This section is designed to give the reader an overall summary of the monograph contents, indicating the extent of phytochemical, pharmacological and clinical data available for the herbal ingredient, whether or not proposed herbal uses are justified, concerns over safety and, based on this information, whether or not the herbal ingredient is considered suitable for use as a herbal medicine
Species (Family)	Preferred botanical name with authority, together with the plant family.
Synonym(s)	Other common or botanical names.
Part(s) Used	Plant part(s) traditionally used in herbal medicine.
Pharmacopoeial and Other Monographs	Key pharmacopoeial monographs and texts on herbal medicines.
UK Legal Category	Legal category of the herb with respect to licensed products. For the majority of herbal ingredients this will be the General Sales List (GSL).
Constituents	Main documented chemical constituents grouped into categories such as alkaloids (type specified), flavonoids, iridoid glycosides, saponins, tannins, triterpenes, volatile oil and other constituents for miscellaneous and minor chemical components.

table continues

Chemical structural formulae	Chemical structural formulae are included for key constituents of herbal ingredients for virtually every monograph. This information supplements the textual information on constituents.
Quality of plant material and commercial products	This section has been included for several herbal ingredients commonly encountered in commercial products. It describes studies examining the variation in phytochemical content of crude plant material and marketed products and other aspects relating to product quality, such as differences between actual and labelled content of commercial products.
Food Use	Provides an indication as to whether the herbal ingredient is used in foods. The Council of Europe (COE) category, which reflects the opinion of the COE on the suitability of the herbal ingredient for use as a food flavouring, is quoted where applicable.
Herbal Use	States the reputed actions and uses of the herbal ingredients, based on information from several sources. In some instances, current investigations of particular interest are included.
Photographs	Provided for most of the monographs for the crude drug substance and the plant from which it originates. As we do not provide botanical, macroscopical or microscopical descriptions, these photographs are for illustrative purposes only and are not intended to be used for identification purposes.
Dosage	States the traditional dose of the herbal ingredient, mainly from the British Herbal Pharmacopoeia (BHP), German Commission E and European Scientific Co-operative on Phytotherapy (ESCOP) monographs, giving doses for plant part used (e.g. herb, rhizome, leaf), liquid extract and infusion. Where possible, dosages typically used in clinical trials are included.
Pharmacological Actions	Describes any documented pharmacological actions for the herbal ingredient. This is further divided into a section on *In vitro and animal studies* and a *Clinical studies* section, which describes studies involving humans.
Side-effects, Toxicity	Details documented side-effects to the herbal ingredient and toxicological studies. If side-effects or toxicity are generally associated with any of the constituents in the herbal ingredient, or with its plant family, then these are mentioned here. *See also* Table 1 and Table 2 in the Introduction.
Contra-indications, Warnings	Describes potential contra-indications and potential side-effects, and individuals who may be more susceptible to a particular side-effect. This section should be used in conjunction with Appendices 1–3. Comments on Pregnancy and lactation are included; a summary is provided in Table 3 of the Introduction.
Preparations	Describes product information from over 35 countries. Arranged in two sections, the first section lists by country the proprietary names (product names) of preparations containing the single herbal ingredient described in the monograph. The second section lists by country products that contain multiple ingredients including the herbal ingredient described in the monograph. Specific suppliers of preparations are shown in Appendix 4 along with the supplier contact information in Appendix 5.
References	References are included at the end of the text on each monograph. There is considerable literature on herbal plants and general references have been selected for use with the handbook. These General References, referred to as G1 to G88, are listed after the Introduction. For some well-known herbal ingredients only general references are cited. The majority of the monographs also contain specific references which are cited at the end of each monograph.

Introduction

A general disillusionment with conventional medicines, coupled with the desire for a 'natural' lifestyle has resulted in an increasing utilisation of complementary and alternative medicine (CAM) across the developed world.

A study of long-term trends in the use of CAM therapies in the United States of America reported that the use of CAM therapies has increased steadily since the 1950s.[1] Use of CAM has increased independent of gender, ethnicity and level of education, but is more common in younger people. The use of herbal medicine increased particularly in the 1970s and then again in the 1990s. The report concluded that the continuing demand for CAM will affect delivery of healthcare for the foreseeable future. More recent studies have confirmed that the prevalence of CAM use has remained stable with about a third of US adults reported to use CAM therapies.[2, 3] The ten top-selling herbal products in the US in 2004 have been reported as garlic, echinacea, saw palmetto, ginkgo, soy, cranberry, ginseng, black cohosh, St John's wort and milk thistle.[4] The continuing use of CAM has also been reported in South Australia where in 2004, CAMs were reportedly used by over 50% of the population.[5] Several other studies have documented the growing use of CAM in the United Kingdom, with the most common complementary therapies reported as acupuncture, homeopathy, herbal medicine and manipulative therapies, chiropractic and osteopathy.[6]

Estimates of the prevalence of CAM utilisation amongst the general population in the UK range from 10.6%, for use of a limited list of CAM therapies, to 46.6% for use of CAM therapies or over-the-counter (OTC) CAM products.[7, 8] In its report on complementary and alternative medicine, the House of Lords Select Committee on Science and Technology's Subcommittee on Complementary and Alternative Medicine highlighted the lack of comprehensive information on the use of herbal medicines in the UK.[9] Estimates of herbal medicine use are available, but it is difficult to gauge usage accurately as many products are considered to be food supplements. Nevertheless, a national telephone survey of a nationally representative sample of 1204 British adults found that around 7% of those contacted had used herbal medicines in the previous year.[10] In another cross-sectional study, over 5000 randomly selected adults in England were sent a postal questionnaire on their use of CAM.[7] Around 20% of the respondents had bought an over-the-counter herbal remedy in the previous 12 months.

Estimates of expenditure on herbal medicines vary, but data generally show that the global market for herbal products has grown rapidly in the past decade. In the USA, annual retail sales of herbal medicines were estimated to be US$ 1.6 billion in 1994,[11] and almost US$ 4 billion in 1998.[12] However, since then there have been reports that the US market has levelled off and in some cases declined.[13] Retail sales of herbal products in the European Union (EU) were estimated to be US$ 7000 million in 1996.[14] A detailed analysis of the European herbal medicines market reported that Germany and France make up more than 70% of the market share.[15] In 1997, total sales of herbal products (using wholesale prices) were US$1.8 billion in Germany and US $1.1 billion in France. In the UK, retail sales of herbal products are reported to have increased by 43% in the period from 1994 to 1998, with retail sales of licensed herbal medicinal products reported to be £50 million in 1998.[9]

Market reports from 2003 indicated a growth in the UK sales of complementary medicines of almost 60% over the previous five years with an estimated value of £130 million. Herbal medicines were reported to represent 60% of the market.[16] Recent reports indicate that the UK market has continued to expand by 45% from 1999 to 2004, with sales of herbal medicines accounting for more than 50%, having risen by 16% since 2002.[17]

These figures demonstrate that herbal medicinal products are being used increasingly by the general public on a self-selection basis to either replace or complement conventional medicines. Against this background of increasing usage of herbal medicines by the public, a number of major public health issues have raised concerns about these products and have highlighted the need for healthcare professionals to have up-to-date scientific information on the quality, safety and efficacy of these products. The substitution of toxic *Aristolochia* species in traditional Chinese medicines (TCM) has resulted in cases of serious renal toxicity and renal cancer in Europe, China and America.[18] The emergence of interactions between *Hypericum perforatum* (*see* St John's wort) and certain prescription medicines has necessitated regulatory action world-wide.[19]

Serious cases of liver damage including a number of fatalities associated with the use of *Piper methysticum* (*see* Kava) have led to restrictions on its use in many countries.[20] Frequent reports of the presence of toxic heavy metals and pharmaceutical substances in Ayurvedic and traditional Chinese medicines reflect a global problem of poor quality of many herbal products.[21, 22]

Pharmacists need to be able to advise the consumer on the rational and safe use of all medicines. Studies in the UK, Australia and the US show that pharmacists are frequently involved in the supply of herbal medicines.[23–26]

In order to fulfil this role, pharmacists need to be knowledgeable about herbal medicines and should have access to reliable information in order to advise patients and the public on the safe, effective and appropriate use of herbal preparations. The need to be reliably informed of the quality, safety and efficacy of herbal medicines has been highlighted.[27–29] Also, many other healthcare professionals are becoming increasingly aware of their patients' use of herbal medicines and need to be informed of the suitability of these products for use as medicines.

This handbook brings together in one text a series of monographs on 152 herbs commonly present in herbal medicinal products sold through pharmacies in the UK. Three appendices are also presented, grouping together herbs with specific actions, and highlighting potential interactions with conventional medicines.

As a preface to the monographs, an overview of UK and European legislation concerning herbal products is provided, together with issues pertaining to their quality, safety and efficacy. In addition to retail purchase, herbs can be obtained by picking the wild plant or from a herbal practitioner. This handbook does not discuss the self-collection of plant material for use as a herbal remedy or the prescribing of herbal medicines by herbal practitioners.

Herbal Medicines and Phytotherapy

Herbal medicines are also referred to as herbal remedies, herbal products, herbal medicinal products, phytomedicines, phytotherapeutic agents and phytopharmaceuticals. The use of herbal medicines in an evidence- or science-based approach for the treatment and prevention of disease is known as (rational) phytotherapy. This approach to the use of herbal medicines contrasts with traditional medical herbalism which uses herbal medicines in a holistic manner and mainly on the basis of their empirical and traditional uses. Although these two approaches – traditional/holistic and rational/evidence-based – are entirely different, in some instances they use the same terminology. For example, traditional herbalism is also described as 'phytotherapy' and refers to preparations of plant material as 'herbal medicines'. Today, a continuum between these approaches exists and many herbalists also use scientific evidence to support their traditional use of herbal medicines. Plants have been used medicinally for thousands of years by cultures all over the world. According to the World Health Organization, 80% of the world's population uses plant-based remedies as their primary form of healthcare;[30] in some countries, herbal medicines are still a central part of the medical system, such as Ayurvedic medicine in India and traditional Chinese medicine in China. Herbal medicine has a long history and tradition in Europe.

Herbal medicines and homeopathic remedies are often mistaken by the layperson to be similar. However, homeopathy is based on the principle of 'like should be treated by like', and involves the administration of minute doses of remedies that, in larger doses, produce symptoms in a healthy person mimicking those expressed by people who are ill. Many, but not all, homeopathic remedies originate from plants. By contrast, herbal medicine (phytotherapy) involves the use of dried plant material or extracts of plant parts in therapeutic doses to treat the symptoms exhibited. In this latter respect, it is similar to conventional medicine.

Regulatory Controls on Herbal Medicines

Herbal medicinal products in Europe

Herbal products are available in all Member States of the European Union (EU), although the relative size of their markets varies between countries. Since the late 1980s, the regulation of herbal products has been a major issue within the EU because of the differences between Member States in the way herbal products are classified and the difficulties this might present in the completion of the single market for pharmaceuticals.

According to Council Directive 2001/83/EEC, as amended, a medicinal product is defined as 'any substance or combination of substances presented as having properties for treating or preventing disease in human beings or any substance or combination of substances which may be administered to human beings with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a diagnosis.'[31]

Herbal products are considered as medicinal products if they fall within the definition of the Directive. However, the legal classification is complicated by the fact that in most Member States herbal products are available both as medicinal products with therapeutic claims and also as food/dietary supplements without medicinal claims. The situation is further complicated in that some Member States, including the UK (*see* Current regulatory position of herbal products in the UK), have national provisions which permit certain herbal medicinal products to be exempt from the licensing provisions under specific conditions. In general, in all Member States, herbal products are classified as medicinal products if they claim therapeutic or prophylactic indications.

The advent of the new pan-European marketing authorisation system in 1993 raised questions with regard to herbal products and, in particular, concerns that major differences in their classification/assessment would hinder free circulation within the EU. The new systems for marketing authorisations involve three procedures: centralised, decentralised (mutual recognition) and national.[32, 33] The centralised procedure is mandatory for biotechnology products and since November 2005 was mandatory for orphan medicinal products and any medicinal product for human use containing new active substances (i.e. one not previously authorised in the Community) for the treatment of AIDS, cancer, neuro-degenerative disease and diabetes.[34] The decentralised procedure or mutual recognition system involves agreement of assessment between the Member States involved; this procedure became compulsory from January 1998, for products requesting authorisation in more than one Member State. Since then, simultaneous national applications have been possible, but the mutual recognition system automatically becomes involved once an authorisation has been granted in the first Member State. The original intention was to retain existing national procedures for medicinal products requesting authorisation in a single Member State only. However, the European Commission agreed that national procedures could continue for bibliographic applications, including those for herbal products until the harmonisation issues could be resolved.

In 1997, upon the initiative of the European Parliament, the European Commission and the (then) European Medicines Evaluation Agency (EMEA), now European Medicines Agency, an *ad hoc* Working Group on Herbal Medicinal Products (HMPWG) was established at the EMEA. The main thrust of the HMPWG was the protection of public health by preparing guidance to help facilitate mutual recognition of marketing authorisations in the field of herbal medicines, and to minimise CHMP (Committee on Human Medicinal Products) formerly the Committee on Proprietary Medicinal Products (CPMP) arbitrations.

A major study undertaken by the AESGP (Association of the European Self-medication Industry) in 1998 at the request of the European Commission confirmed the different approaches taken by Member States in the regulation of herbal medicinal products.[35] Different traditions in the therapeutic use of herbal preparations, coupled with different national approaches to their assessment, have resulted in differences in the availability of some herbal medicines. For example, ginkgo (*Ginkgo biloba*) is available as a prescription-only medicine in some EU countries, but as a food supplement in others. Similarly, St John's wort (*Hypericum perforatum*) is accepted as a treatment for depression in some Member States, but not in others.

The AESGP study revealed that, in general, herbal medicinal products were either fully licensed with efficacy proven by clinical trials or by bibliography (in accordance with Article 10.1 a (i) of Council Directive 2001/83/EC), or that herbal products had a more or less simplified proof of efficacy, according to their national use. Furthermore, the study found major discrepancies between Member States in the classification of individual herbal preparations and products into one of these categories, as well as in the requirements for obtaining a marketing authorisation (product licence). The report highlighted the need for clarification

of the regulatory framework and harmonisation of the regulatory requirements to ensure that herbal medicinal products could have access to the single market for pharmaceuticals.

An important initiative in the harmonisation process has been the formation of the European Scientific Cooperative on Phytotherapy (ESCOP), an organisation representing national associations for phytotherapy. ESCOP was founded in 1989 by six EU national scientific associations with the objective of establishing a scientific umbrella organisation to provide harmonised criteria for the assessment of herbal medicinal products, to support scientific research and contribute to the acceptance of phytotherapy in Europe.[36,37]

ESCOP now comprises 13 national associations across Europe, and the American Botanical Council. The ESCOP Scientific Committee has published 80 monographs for individual herbal drugs; the monographs follow the European Summary of Product Characteristics (SPC) format.[38] The EMEA Herbal Medicinal Products Working Party (HMPWP) formerly used the ESCOP monographs as a basis for its work in developing core SPCs from ESCOP monographs. The HMPWP has now been superseded by the Herbal Medicinal Products Committee (HMPC) as discussed below and the collaboration with ESCOP continues in accordance with the new EU regulations.

New regulations for traditional herbal medicinal products in the EU

From the late 1980s, the need for a new regulatory framework for herbal products has been under discussion supported by the European Parliament and the European Commission. It was generally accepted that a significant number of herbal medicinal products did not fulfil the requirements for marketing authorizations. In September 1999, the European Pharmaceutical Committee set up a working group of Member States to investigate the possibility of a directive for traditionally used medicines. Work commenced in April 2000 and a new EU Directive on Traditional Herbal Medicinal Products 2004/24/EC came into force in April 2004 requiring Member States to implement registration schemes by October 2005.[39] The aim is to remove the differences which create obstacles to the free movement of medicinal products in the EU, while ensuring protection for public health. For unlicensed herbal medicines legally on the market on 30 April 2004, the Directive provides a seven-year transitional period to allow companies time to meet the new requirements. The new Directive provides a framework for the regulation of traditionally used herbal medicinal products requiring them to meet specific and appropriate standards of safety and quality and for the product to be accompanied by suitable information to ensure its safe use. Registered products are required to be suitable for self-medication without the need for the intervention of a medical practitioner. The normal requirement for medicines to be proven to be efficacious, as required under Directive 2001/83/EC for a marketing authorisation, is replaced by a requirement to demonstrate 30 years' traditional use for the required medicinal indication; at least 15 years of this usage must have been within the EU.

Registration applications have to include a bibliographic review of the safety data associated with the use of the herbal product in a particular indication. In addition, this review will need to be accompanied by an expert report on the safety data submitted. The normal quality requirements applicable to licensed medicines will apply, including good manufacturing practice (GMP) and European Pharmacopoeia standards. Labelling and package leaflets for registered products will be required to include information and instructions about the safe use of the product and will include a statement to the effect that the product is based on long-standing use. In addition to the herbal ingredients, vitamins and minerals can be added provided that they are ancillary to the herbal active ingredients. Manufacturers will be required to have in place an adequate pharmacovigilance system to maintain records of all suspected adverse drug reactions (ADRs) occurring world-wide and will have to report all ADRs to the national regulatory licensing authority.

The Directive established a new European Committee at the EMEA, the Committee on Herbal Medicinal Products (HMPC) with responsibilities to prepare Community monographs and a Community list of herbal substances. A Community herbal monograph comprises the committee's scientific opinion on a given herbal medicinal product, based on its evaluation of available scientific data (well-established use) or on the historic use of that product in the European Community (traditional use). For some herbal medicinal products, the Community monograph will cover both well-established use and traditional use. The Community monographs are intended to assist harmonisation of requirements for 'bibliographic' marketing authorisation applications. When the HMPC has produced a draft Community monograph it is released for public consultation on the EMEA website, usually for a period of three months. The comments received are subsequently reviewed and the final version of the Community herbal monograph is published.

The Community list will contain, for each herbal substance or preparation, the indication, the specified strength and the posology, the route of administration and any other information necessary for the safe use of the herbal substance or preparation used as an ingredient of a traditional medicinal product. The Community list will provide a harmonised approach at EU level for providing information on substance(s) or preparation(s) that constitute traditional herbal medicinal products. The list will cover substances and preparations that have been in medicinal use for a sufficiently long time, and therefore considered not to be harmful under normal conditions of use. List entries are also released for public consultation on the EMEA website, usually for a period of three months. Applicants for traditional registrations can refer to the list rather than have to provide evidence of traditional use and safety thus further simplifying the registration procedure. Draft and adopted Community monographs are available on the EMEA website.[40]

A simplified registration scheme was introduced in the UK in October 2005 for traditional herbal medicinal products. A new advisory committee, the Herbal Medicines Advisory Committee (HMAC), has been established to advise Health Ministers on issues relating to registration of traditional herbal medicinal products and the safety and quality of unlicensed herbal remedies.

Current regulatory position of herbal products in the UK

Herbal products are available in the UK through various retail outlets, such as pharmacies, health-food shops, mail order companies, supermarkets, department stores and, increasingly, via the internet. Some herbal products consist solely of loose, dried plant material; others are presented as pre-packaged formulated products in a variety of pharmaceutical forms for both internal (tablets, capsules, liquids) and external use (creams, ointments) and may contain one or several herbal ingredients which may be dried herbs or their extracts. The current regulatory position is complicated by the fact that herbal products can fall into one of three categories: licensed herbal products, those

exempt from licensing and those marketed as food supplements. In addition, from November 2005, the registration procedure for traditional herbal medicinal products has introduced a further category, that of 'registered products'.

The majority of herbal products are marketed without medicinal claims either exempt from licensing (*see* Herbal remedies exempt from licensing) or as food supplements. Those supplied as food supplements are controlled under food legislation whilst those exempt from licensing are controlled under medicines legislation. Difficulties in defining the status of products occupying the borderline between medicines and foods have resulted in similar products being marketed in both these categories. Provided the products were marketed without reference to medicinal claims, the Medicines and Healthcare products Regulatory Agency (MHRA; formerly Medicines Control Agency (MCA)), the government body responsible for regulating medicinal products has, in the past, generally been satisfied that the products were not subject to medicines legislation.[41] However, implementation of the definition of a medicinal product in accordance with EC Directives has meant that greater emphasis is now being placed on the nature of the herbal ingredients being supplied as food supplements.

Licensed herbal medicinal products

Almost all of the licensed herbal medicines on the UK market have been available for some time and most originally held Product Licences of Right (PLR). Following the implementation of the UK Medicines Act in 1971, Product Licences of Right were issued to all medicinal products already on the market in September 1971, however, scientific assessment was not undertaken at the time the PLR was granted. A subsequent review of all PLRs for safety, quality and efficacy took place culminating in 1990. During the UK review of herbal medicinal products holding a PLR, the Licensing Authority agreed to accept bibliographic evidence of efficacy for herbal medicinal products which were indicated for minor, self-limiting conditions.[42] No evidence was required from new clinical trials provided the manufacturers agreed to label their products as 'a traditional herbal remedy for the symptomatic relief of …' and to include the statement 'if symptoms persist consult your doctor'. The Licensing Authority considered it inappropriate to relax the requirements for proof of efficacy for herbal medicinal products indicated for more serious conditions. Thus, evidence was required from controlled clinical trials for herbal medicinal products indicated for conditions considered inappropriate for self-diagnosis and treatment. Many features of the new traditional use registration scheme are similar to those applied during the review of PLRs.

The MHRA regulates medicinal products for human use in accordance with The Medicines (Marketing Authorisations etc.) Amendment Regulations 2005, (The Regulations)[43] and the Medicines Act 1968.[44] The Medicines Act and secondary legislation made under it remain the legal basis for other aspects of medicines control including manufacturer and wholesale dealers' authorisations, controls on sale and supply and controls on promotion. Further explanation may be obtained by reference to a chapter on herbal remedies in *Dale and Appelbe's Pharmacy Law and Ethics*.[45]

Applications for marketing authorisations (product licences) for new herbal products are assessed by the MHRA for quality, safety and efficacy in accordance with EC and UK legislation. Specific EC guidelines exist on the quality, specifications and manufacture of herbal medicinal products.[46–48] Few applications for new marketing authorisations are successful and the difficulties faced by herbal manufacturers in fulfilling the regulatory requirements have led to the development of the new simplified traditional use registration scheme outlined above. It will continue to be possible to obtain a marketing authorisation for a herbal medicinal product provided that the required data on safety, quality and efficacy can be demonstrated.

Herbal remedies exempt from licensing

Under the Medicines Act, herbal remedies manufactured and sold or supplied in accordance with specific exemptions set out in Sections 12(1) or (2) or Article 2 of the Medicines (Exemptions from Licences) (Special and Transitional Cases) Order 1971 (SI 1450)[49] are exempt from the requirement to hold product licences. The exempt products are those compounded and supplied by herbalists on their own recommendation, those comprised solely of dried, crushed or comminuted plants sold under their botanical name with no written recommendations as to their use, and those made by a holder of a Specials Manufacturing Licence on behalf of a herbalist.

The exemptions are intended, for example, to give herbal practitioners the flexibility they need to prepare their own remedies for individual patients without the burden of licensing, and to enable simple dried herbs to be readily available to the public. Supply of herbal remedies by herbal practitioners is not affected by the new regulations on traditional medicines. Proposals for the reform of the regulation of unlicensed herbal remedies made up to meet the needs of individual patients are currently under consideration.[50]

At the present time, most manufactured over-the-counter herbal medicines in the UK are sold under the exemptions provided for by Section 12(2) of the Medicines Act. It has been recognised for some time that the arrangements for unlicensed herbal medicinal products do not afford sufficient protection for public health and that there is a need to improve the regulatory position. The MHRA is now of the view that the present regulatory arrangements for unlicensed herbal medicines have significant weaknesses.[9] The regime for unlicensed herbal products is considered not to provide sufficient protection or information for the public and there are no specific safeguards in place to ensure adequate product quality and safety.[51]

The all party House of Lords Select Committee on Science and Technology concluded: *'We are concerned about the safety implications of an unregulated herbal sector and we urge that all legislative avenues be explored to ensure better control of this unregulated sector in the interests of public health.'*[9]

Evidence of the risks to public health have continued to emerge and in September 2004 the Committee on Safety of Medicines (CSM) repeated an earlier warning about their concerns in relation to the poor quality of some traditional Chinese medicines on the UK market.[52]

The MHRA has indicated that it is the Government's intention that, following the transitional period of the Traditional Use Directive, Section 12 (2) would cease to provide a regulatory route by which manufactured herbal medicinal products can reach the market place without a traditional registration or product licence.[53]

Control of herbal ingredients in the UK

Most of the herbal ingredients used in licensed herbal medicines have been used as traditional remedies for centuries without major

safety problems, and the majority is included in the General Sales List (GSL).[54] Potentially hazardous plants such as digitalis, rauwolfia and nux vomica are specifically controlled under the Medicines Act as prescription only medicines (POM),[55] and thus are not available other than via a registered medical practitioner. In addition, certain herbal ingredients are controlled under The Medicines (Retail Sale and Supply of Herbal Remedies) Order 1977 SI 2130.[56] This Order (Part I) specifies 25 plants which cannot be supplied except via a pharmacy, and includes well-known toxic species, such as *Areca*, *Crotalaria*, *Dryopteris* and *Strophanthus*. In Part II, the Order specifies plant species, such as *Aconitum*, *Atropa*, *Ephedra* and *Hyoscyamus*, which can be supplied by 'herbal practitioners', and in Part III defines the dosages and routes of administration permitted.

Legislation has been introduced to prohibit the use of *Aristolochia* species or species likely to be confused with *Aristolochia* in unlicensed medicines.[57] These measures were introduced in the wake of cases of serious toxicity and evidence showing widespread substitution of certain ingredients in traditional Chinese medicines with *Aristolochia* (*see* Quality, Safety and Efficacy of Herbal Medicines).

Following cases of serious liver damage suspected to be associated with its consumption *Piper methysticum* (*see* Kava) was prohibited in unlicensed herbal medicines in January 2003.[58] The MHRA has also announced the need to update the list of herbal ingredients subject to restrictions or prohibitions in use in unlicensed medicines to take account of the herbal ingredients used in traditional Chinese and Ayurvedic medicines.[59]

Regulatory control of herbal medicines world-wide

The World Health Organization (WHO) has conducted a recent global survey on the regulatory control of herbal medicines and has reported findings from 141 countries.[60] This work provides a valuable update to the earlier WHO reviews and illustrates the wide differences in the approach to regulation between these countries[61,62] The recent survey confirms that during the past four years many countries have established, or initiated, the process of establishing national policy and regulations regarding herbal medicines. The most important challenges faced by countries were those related to regulatory status, assessment of safety and efficacy, quality control and safety monitoring. In response to requests from Member States, WHO has resolved to provide technical support for the development of methodology to monitor or ensure product safety, efficacy and quality, preparation of guidelines, and promotion of information exchange. WHO guidelines have recently been developed in a number of important areas including consumer information, pharmacovigilance and good agricultural and collection practices (GACP).[63–65]

Herbal products are well established as phytomedicines in some countries, whereas in others they are regarded as foods, and therapeutic claims are not allowed. In the context of this book, it should be noted that many of the herbs included in the monographs are of economic importance in some non-European countries, particularly Australia, Canada and the USA.

In Australia, therapeutic goods for human use which are imported or manufactured are subject to the Therapeutic Goods Act, 1989 and all therapeutic goods imported into, supplied in or exported from Australia must be included in the Australian Register of Therapeutic Goods (ARTG).[66] Herbal medicines, including traditional medicines such as Ayurvedic medicines and traditional Chinese medicines (TCM) are regulated as complementary medicines. For the purpose of labelling requirements, herbs are included in the List of Australian Approved Names for Pharmaceutical Substances, which is published by the Therapeutic Goods Administration. The Australian system has a two-tiered approach based on risk. Low risk medicines, which include most complementary medicines, are included in the ARTG as listed medicines. These medicines are not evaluated before they are released on to the market, but are checked to ensure that they comply with certain legislative requirements. Listed medicines have limited therapeutic indications, for example health enhancement, reduction in risk of a disease, disorder or condition, reduction in frequency of a discrete event, aiding or assisting management of a symptom, disease, disorder or condition, relief of symptoms. Indications and claims referring to treatment, management, cure or prevention of a disease, disorder, or condition or reference to a serious form of a disease are generally not permitted for listed medicines. Those medicines deemed to be higher risk are assessed individually for safety, quality and efficacy prior to marketing.

In Canada, new regulations, the Natural Health Products Regulations, came into force in January 2004.[67] Products that fall within the new regulations include herbal remedies, homeopathic medicines, vitamins, minerals, traditional medicines, probiotics, amino acids and essential fatty acids. The new regulations introduce a system of product licensing, site licensing, GMP, adverse reaction reporting and requirements for labelling. Persons marketing products before January 2004 have a transition period of two years to comply with the site licence requirements of the regulations and those products with a valid Drug Identification Number, from the previous regulatory regime, have six years to obtain a product licence under the new regulations. Product licence applications are assessed for safety and efficacy and different types of claims can be proposed, e.g. therapeutic claims, risk reduction claims or structure–function claims supported by traditional use or non-traditional use.

In the USA, the majority of medicinal herbs and their products are regulated like foods as dietary supplements, under the 1994 Dietary Supplement Health and Education Act (DSHEA).[68,69] Whilst medicinal claims cannot be made for the products, labelling may describe effects on general well-being. Unlike new medicines, dietary supplements do not generally have to go through review by the Food and Drug Administration for safety and effectiveness or be approved before they can be marketed. However, manufacturers must provide premarket notice and evidence of safety for any supplements they plan to sell that contain dietary ingredients that were not on the market before DSHEA was passed. Concerns have been raised about the effectiveness of the DSHEA legislation following the emergence of major safety issues arising with unsafe ingredients e.g. ephedra, lack of GMP, poor labelling and inadequate reporting of adverse reactions.[69,70] In response, the FDA has announced the development of strategies to monitor and evaluate product and ingredient safety; to assure product quality (current good manufacturing practice regulations (cGMP); and to improve product labelling.[71,72]

It is apparent that not only is the regulation of medicinal herbs different from one country to another, but also that the regulatory processes are not necessarily ideal and are under current review.

Quality, Safety and Efficacy of Herbal Medicines

In order to ensure public health, medicinal products must be safe, efficacious and of suitable quality for use. To obtain a marketing authorisation (product licence) within the EU, manufacturers of

herbal medicinal products are required to demonstrate that their products meet acceptable standards of quality, safety and efficacy.

Quality

Over the past decade the quality of herbal products has continued to be a major concern. The importance of quality in ensuring the safety and efficacy of herbal products has been reviewed extensively.[22, 73–78]

Problems with unregulated herbal products

The vast majority of quality-related problems are associated with unregulated herbal products. There is substantial evidence that many ethnic medicines, in particular, those used in traditional Chinese medicine (TCM) and traditional Asian medicines (Ayurvedic and Unani), lack effective quality controls and may give rise to serious public health concerns. The problems include deliberate or accidental inclusion of prohibited or restricted ingredients, substitution of ingredients, contamination with toxic substances and differences between the labelled and actual contents. These problems are further compounded by demand outstripping supply of good quality ingredients, confusing nomenclature over plant species, cultural differences of view over toxicity and traditional practices such as substituting one ingredient for another having a reportedly similar action.

Although individual herbs present in traditional Chinese medicines and traditional Asian medicines are not the subject of monographs in this book, they do illustrate the problems that may be associated with the quality and safety of herbal medicines.

Substitution and adulteration

Aristolochia Exposure to *Aristolochia* species in unlicensed herbal medicines has resulted in cases of nephrotoxicity and carcinogenicity in Europe, China, Japan and the USA.[18] Concerns were first raised about the effects of products containing aristolochic acids in Belgium where, since 1993, over 100 cases of irreversible nephropathy have been reported in young women using a preparation claimed to aid weight loss. The nephrotoxicity was traced to the inadvertent use of the toxic *Aristolochia fangchi* root in the formulation as a substitute for *Stephania tetrandra*. Aristolochic acids, the toxic components of *Aristolochia* species, are known to be nephrotoxic, carcinogenic and mutagenic. The International Agency for Research on Cancer classifies products containing *Aristolochia* species as human carcinogens.[79] Several of the Belgian patients have subsequently developed urothelial cancer as a result of exposure to the toxic aristolochic acids.[80–84]

Seven cases of nephropathy involving substitution of *Aristolochia fangchi* and *Stephania tetrandra* have been reported in France.[18] Toxicity has also resulted from the substitution of *Aristolochia manshuriensis* stem for the stem of *Clematis* and *Akebia* species.[18] In the UK, two such cases of end-stage renal failure were reported in 1999.[85, 86] Other cases have been reported in China (17 cases with 12 fatalities) and Japan (ten cases of renal failure).[18] Also, the FDA has reported two cases of serious renal disease due to *Aristolochia* being substituted for *Clematis* species in a dietary supplement.[87]

Substitution of one plant species for another, often of a completely different genus, is an established practice in TCM. Furthermore, herbal ingredients are traded using their common Chinese Pin Yin names, and this can lead to confusion. For example, the name Fang ji can be used to describe the roots of *Aristolochia fangchi*, *Stephania tetrandra* or *Cocculus* species, and the name Mu Tong can be used to describe the stem of *Aristolochia manshuriensis*, *Clematis* or *Akebia* species. The widespread substitution with *Aristolochia* species in TCM products available in the UK was shown in a MHRA study which reported the presence of aristolochic acids in at least 40% of TCM products containing Fang ji and Mu Tong.[88]

The problems associated with *Aristolochia* have prompted regulatory action world-wide and new legislation has been introduced in the UK to prohibit the use of *Aristolochia* species in unlicensed medicines in the UK.[57]

Despite warnings and an import alert issued by the US FDA in 2001, products containing aristolochic acid were found to be available on US websites in 2003.[89] The MHRA has reported that it continues to find products containing *Aristolochia* on the UK market. In 2003, a product called Xie Gan Wan was found to contain aristolochic acids and in December 2004, tablets called Jingzhi Kesou Tanchuan were found to contain *Aristolochia* fructus.[90] Also in December 2004, the Hong Kong authorities alerted other health authorities to a product Shen Yi Qian Lie Hui Chin that contained aristolochic acids. In December 2005, MHRA issued a warning about the possible presence of *Aristolochia* species in African herbal remedies available in the UK.

Digitalis Cases of serious cardiac arrhythmias were reported in the USA in 1997 following the accidental substitution of plantain with *Digitalis lanata*.[91] Subsequent investigation revealed that large quantities of the contaminated plantain had been shipped to more than 150 manufacturers, distributors and retailers over a two-year period.

Podophyllum Fourteen cases of podophyllum poisoning have been reported from Hong Kong following the inadvertent use of the roots *Podophyllum hexandrum* instead of *Gentiana* and *Clematis* species.[92] It is reported that this accidental substitution arose because of the apparent similarity in morphology of the roots.

Aconitum Cases of cardiotoxicity resulting from the ingestion of *Aconitum* species used in TCM have been reported from Hong Kong.[93] In TCM, *Aconitum* rootstocks are processed by soaking or boiling them in water in order to hydrolyse the aconite alkaloids into their less toxic aconine derivatives. Toxicity can, however, result when such processes are uncontrolled and unvalidated. In the UK, the internal use of aconite is restricted to prescription only.

Star Anise The dangers of confusing Chinese (*Illicium verum* Hook.f.) and Japanese star anise (*Illicium anisatum* L.), have been known for many years as the dried fruits cannot be distinguished through visual examination. Japanese star anise is similar to the Chinese variety but has been reported to cause neurologic and gastrointestinal toxicities due to the presence of anisatin.[94, 95] In 2001 cases of poisoning were reported in the Netherlands, Spain and France where Japanese star anise had been accidentally used in place of Chinese star anise.[96–98] Several cases were epileptic-type seizures in babies who had been given star anise infusions. This led to over 50 cases of poisoning being reported, but there was no evidence that the affected products had been imported into the UK. In the US, seven cases of adverse neurologic reactions have been reported among infants aged two weeks to three months who were exposed to star anise tea.[99]

Adulteration with heavy metals/toxic elements and synthetic drugs

The adulteration of ethnic medicines with heavy metals/toxic elements and synthetic drugs continues to be a major international problem. A comprehensive review in 1992 summarised test results on products and case histories of patients who had experienced toxic effects.[72] Similar findings continue to be reported and the potential impact on public health is significant.[22] In most cases involving synthetic drugs, the drugs are undeclared in the product and only come to light when the user experiences adverse effects which are sufficiently serious to warrant medical intervention. Exposure to the undeclared drug is revealed in the subsequent investigation of the clinical case. Of particular concern is the deliberate addition of closely related derivatives of pharmaceutical drugs, for example the use of nitrosofenfluramine instead of fenfluramine in weight-loss products.[22]

The situation with the heavy metals/toxic elements differs in that whilst these ingredients may arise from the plant ingredients themselves or be introduced as trace contaminants during processing, they are also frequently added intentionally and declared as ingredients within some TCM and Asian medicine formulations. The Chinese Pharmacopoeia, for example, includes monographs for realgar (arsenic disulfide), calomel (mercurous chloride), cinnabaris (mercuric sulfide) and hydrargyri oxydum rubrum (red mercuric oxide), and includes formulations for nearly 50 products that include one or more of these substances.[100]

A US survey in 1998 reported widespread inconsistencies and adulterations in imported Asian medicines.[101] Of 260 imported products tested, at least 83 (32%) contained undeclared pharmaceuticals (most commonly ephedrine, chlorphenamine, methyltestosterone and phenacetin) or heavy metals (lead, arsenic or mercury). Another survey found evidence of a continuing problem, with 10% of 500 OTC products testing positive for undeclared drugs and/or toxic amounts of lead, mercury or arsenic.[102]

Elsewhere, health departments have reported similar conclusions based on their findings. A survey conducted in Singapore between 1990 and 1997 on TCM products reported that 42 different products were found to contain excessive amounts of heavy metals (mercury, lead, arsenic) and that 32 different TCM products were found to contain a total of 19 drugs.[103] In total, 93 cases of excessive content of toxic heavy metals and undeclared drugs were detected. The drugs detected included berberine, antihistamines (chlorphenamine, promethazine, cyproheptadine), non-steroidal anti-inflammatory drugs (diclofenac, indometacin, ibuprofen), analgesic antipyretics (paracetamol, dipyrone), corticosteroids (prednisolone, dexamethasone, fluocinonide), sympathomimetics agents (ephedrine), bronchodilators (theophylline), diuretics (hydrochlorthiazide) and the antidiabetic phenformin. A study in Taiwan found that more than 20% of 2609 products were found to be adulterated with synthetic drugs, most commonly caffeine, paracetamol, indometacin and hydrochlorthiazide.[104]

Other examples of adulterated products come from a report from the Singapore Ministry of Health which identified sildenafil in two Chinese proprietary medicines,[105] and a report from the USA FDA which described the recall of a herbal product after traces of chlordiazepoxide were found in the capsules.[106] In 2001, the UK MCA reported presence of mercury (due to the inclusion of cinnabaris) in samples of the product Shugan Wan on the UK market.[90]

Cases of toxicity associated with synthetic drugs present in ethnic medicines include a case of poisoning in Hong Kong resulting from the use of a TCM product containing anticonvulsant agents (phenytoin, carbamazepine and valproate).[107] In 2000, the USA FDA issued a public health warning on five herbal products following adverse effects in patients.[108] The products were found to contain the antihyperglycaemic prescription drugs glibenclamide and phenformin. In March 2001, the UK MCA reported a serious case of hypoglycaemic coma in a patient who had taken a TCM product, Xiaoke Wan, which contained glibenclamide.[109]

Cases of toxicity associated with heavy metals in ethnic medicines include a patient from Taiwan who developed a unique syndrome of multiple renal tubular dysfunction after taking a Chinese herbal medicine contaminated with cadmium.[110] In the USA, two cases of alopecia and sensory polyneuropathy resulting from thallium in a TCM product have been reported.[111] In the UK, cases have been reported of two patients with heavy metal intoxication following ingestion of an Indian remedy containing inorganic arsenic and mercury,[112] and of a patient with lead poisoning after exposure to an Indian medicine containing toxic amounts of lead, arsenic and mercury.[113] In a case reported from Macau, death of a 13-year-old girl from arsenic poisoning has been linked with a Chinese herbal product Niu Huang Chieh Tu Pien.[114]

Evidence of this international problem continues to grow and a substantial body of literature is now available. The adulteration of Chinese and Ayurvedic herbal medicines with synthetic drugs and toxic metals has been extensively reviewed.[21, 22, 115–119]

A survey of 70 Ayurvedic herbal medicinal products available in Boston-area stores (US) found that 20% contained potentially harmful concentrations of lead, mercury and/or arsenic.[120] In response to the many issues arising with herbal products the MHRA has introduced a specific web page Herbal Safety News to provide information on safety alerts.[90] Regular notifications concerning the presence of heavy metals/toxic elements and pharmaceutical drugs in TCM/Ayurvedic products and steroids in dermatological preparations are posted. Of particular concern in recent years has been the discovery of TCM slimming products containing potentially harmful ingredients such as fenfluramine, nitrosofenfluramine, sibutramine, methylphenidate. In March 2004, the Agency was made aware of a UK case of irreversible liver failure suspected to be caused by a product called 'Shubao-Slimming Capsules'. The patient required a liver transplant. The product was labelled as only containing botanical ingredients but was found to contain undeclared nitrosofenfluramine, a drug closely related to the prescription only medicine (POM), fenfluramine. Nitrosofenfluramine is known to be toxic to the liver. Other samples of Shubao tested were found to contain nitrosofenfluramine and/or fenfluramine.

The MHRA has issued guidance to the public alerting them to the specific concerns with TCM slimming products.[90] In September 2004, MHRA issued a press statement warning consumers that the poor quality of some TCM products could pose a health risk to those using them. The MHRA emphasised that it continued to find examples of products containing the prohibited ingredients *Aristolochia* and *Ephedra* as well as products containing heavy metals/ toxic elements, prescription drugs as well as human placenta and bat excreta.[52]

Quality of regulated herbal products

Compared with conventional preparations, herbal medicinal products present a number of unique problems when quality aspects are considered. These arise because of the nature of the

herbal ingredients, which are complex mixtures of constituents, and it is well documented that concentrations of plant constituents can vary considerably depending on environmental and genetic factors. Furthermore, the constituents responsible for the claimed therapeutic effects are frequently unknown or only partly explained and this precludes the level of control which can routinely be achieved with synthetic drug substances in conventional pharmaceuticals. The position is further complicated by the traditional practice of using combinations of herbal ingredients, and it is not uncommon to have five herbal ingredients or more in one product.

In recognition of the special problems associated with herbal medicinal products, the CHMP (formerly CPMP) has issued specific guidelines dealing with quality, specifications and manufacture. These guidelines have recently been updated.[46–48] The EMEA HMPC has also issued guidance on Good Agricultural and Collection Practice (GACP) for starting materials of herbal origin.[121] The CHMP guidelines highlight the need for good control of both the starting materials and the finished product, and emphasise the importance of good manufacturing practice in the manufacture of herbal medicinal products.

The WHO has also published guidelines dealing with the quality control of medicinal plant materials and on good agricultural and collection practices (GACP).[65, 122]

European Pharmacopoeia

Since its creation in 1964, the European Pharmacopoeia (Ph Eur) has devoted part of its work to the establishment of monographs on herbal drugs which are used either in their natural state after drying or extraction, or for the isolation of natural active ingredients. The Ph Eur includes over 120 monographs on herbal drugs, and a similar number of monographs are under development. Many general methods of analysis are also described in the Ph Eur, including tests for pesticides and for microbial contamination.[123]

Herbal ingredients

Control of the starting materials is essential in order to ensure reproducible quality of herbal medicinal products.[22, 78, 124] The following points are to be considered in the control of starting materials.

Authentication and reproducibility of herbal ingredients The problems associated with unregulated herbal products, as illustrated above, highlight the major public health issues that can arise when their herbal ingredients have not been authenticated correctly. Herbal ingredients must be accurately identified by macroscopical and microscopical comparison with authentic material or accurate descriptions of authentic herbs.[125] It is essential that herbal ingredients are referred to by their binomial Latin names of genus and species; only permitted synonyms should be used. Even when correctly authenticated, it is important to realise that different batches of the same herbal ingredient may differ in quality due to a number of factors.

Inter- or intraspecies variation For many plants, there is considerable inter- and intraspecies variation in constituents, which is genetically controlled and may be related to the country of origin.

Environmental factors The quality of a herbal ingredient can be affected by environmental factors, such as climate, altitude and growing conditions.

Time of harvesting For some herbs the optimum time of harvesting should be specified as it is known that the concentrations of constituents in a plant can vary during the growing cycle or even during the course of a day.

Plant part used Active constituents usually vary between plant parts and it is not uncommon for a herbal ingredient to be adulterated with parts of the plant not normally utilised. In addition, plant material that has been previously subjected to extraction and is therefore 'exhausted' is sometimes used to increase the weight of a batch of herbal ingredient.

Post-harvesting factors Storage conditions and processing treatments can greatly affect the quality of a herbal ingredient. Inappropriate storage after harvesting can result in microbial contamination, and processes such as drying may result in a loss of thermolabile active constituents.

Adulteration/substitution Instances of herbal remedies adulterated with other plant material and conventional medicines, and the consequences of this, have been discussed above. In particular, the serious public health consequences that may arise from the substitution of herbal ingredients by toxic *Aristolochia* species have been highlighted. Reports of herbal products devoid of known active constituents have reinforced the need for adequate quality control of herbal remedies.

Identity tests In order to try to ensure the quality of licensed herbal medicines, it is essential not only to establish the botanical identity of a herbal ingredient but also to ensure batch-to-batch reproducibility. Thus, in addition to macroscopical and microscopical evaluation, identity tests are necessary. Such tests include simple chemical tests, e.g. colour or precipitation and chromatographic tests. Thin-layer chromatography is commonly used for identification purposes but for herbal ingredients containing volatile oils a gas–liquid chromatographic test may be used. Although the aim of such tests is to confirm the presence of active principle(s), it is frequently the case that the nature of the active principle has not been established. In such instances chemical and chromatographic tests help to provide batch-to-batch comparability and the chromatogram may be used as a 'fingerprint' for the herbal ingredient by demonstrating the profile of some common plant constituents such as flavonoids.

Assay For those herbal ingredients with known active principles, an assay should be established in order to set the criterion for the minimum accepted percentage of active substance(s). Such assays should, wherever possible, be specific for individual chemical substances and high-pressure liquid chromatography or gas–liquid chromatography are the methods of choice. Where such assays have not been established then non-specific methods such as titration or colorimetric assays may be used to determine the total content of a group of closely related compounds.

Contaminants of herbal ingredients Herbal ingredients should be of high quality and free from insects, other animal matter and excreta. It is not possible to remove completely all contaminants and hence specifications should be set in order to limit them:

Ash values Incineration of a herbal ingredient produces ash which constitutes inorganic matter. Treatment of the ash with hydrochloric acid results in acid-insoluble ash which consists mainly of silica and may be used to act as a measure of soil present. Limits may be set for ash and acid-insoluble ash of herbal ingredients.

Foreign organic matter It is not possible to collect a herbal ingredient without small amounts of related parts of plant or other plants. Standards should be set in order to limit the percentage of such unwanted plant contaminants.

Microbial contamination Aerobic bacteria and fungi are normally present in plant material and may increase due to faulty growing, harvesting, storage or processing. Herbal ingredients, particularly those with high starch content, may be prone to increased microbial growth. It is not uncommon for herbal ingredients to have aerobic bacteria present at 10^2–10^8 colony forming units per gram. Pathogenic organisms including *Enterobacter*, *Enterococcus*, *Clostridium*, *Pseudomonas*, *Shigella* and *Streptococcus* have been shown to contaminate herbal ingredients. It is essential that limits be set for microbial contamination and the Ph Eur now gives non-mandatory guidance on acceptable limits.[123]

Pesticides Herbal ingredients, particularly those grown as cultivated crops, may be contaminated by DDT (dichlorodiphenyltrichloroethane) or other chlorinated hydrocarbons, organophosphates, carbamates or polychlorinated biphenyls. Limit tests are necessary for acceptable levels of pesticide contamination of herbal ingredients. The Ph Eur includes details of test methods together with mandatory limits for 34 potential pesticide residues.[123]

Fumigants Ethylene oxide, methyl bromide and phosphine have been used to control pests which contaminate herbal ingredients. The use of ethylene oxide as a fumigant with herbal drugs is no longer permitted in Europe.

Toxic metals Lead, cadmium, mercury, thallium and arsenic have been shown to be contaminants of some herbal ingredients. Limit tests for such toxic metals are essential for herbal ingredients.

Other contaminants As standards increase for the quality of herbal ingredients it is possible that tests to limit other contaminants such as endotoxins, mycotoxins and radionuclides will be utilised to ensure high quality for medicinal purposes.

Herbal products

Quality assurance of herbal products may be ensured by control of the herbal ingredients and by adherence to good manufacturing practice standards. Some herbal products have many herbal ingredients with only small amounts of individual herbs being present. Chemical and chromatographic tests are useful for developing finished product specifications. Stability and shelf life of herbal products should be established by manufacturers. There should be no differences in standards set for the quality of dosage forms, such as tablets or capsules, of herbal medicines from those of other pharmaceutical preparations.

The quality of an unregulated herbal remedy will not have been assessed by a Regulatory Authority and may thus potentially affect the safety and efficacy of the product. In view of this, it may be concluded that a pharmacist should only sell or recommend herbal medicinal products that hold a product licence or a traditional herbal medicine registration. However, the majority of herbal medicinal products are only available as unlicensed products. When deciding upon the suitability of such products, a pharmacist should consider the intended use and the manufacturer. It is highly likely that unlicensed herbal remedies manufactured by an established pharmaceutical company will have been subjected to suitable in-house quality control procedures.

Safety

As with all forms of self-treatment, the use of herbal medicinal products presents a potential risk to human health.[22, 126] There are concerns that the patient may be exposed to potentially toxic substances either from the herbal ingredients themselves or as a result of exposure to contaminants present in the herbal product. Furthermore, self-administration of any therapy in preference to orthodox treatment may delay a patient seeking qualified advice, or cause a patient to abandon conventional treatment without first seeking appropriate advice. Emerging evidence suggests that herbal medicinal products may in some cases compromise the efficacy of conventional medicines, for example through herb–drug interactions.

The safety of all medicinal products is of the utmost importance. All applications for marketing authorisations for new medicines undergo extensive evaluation of their risks and benefits and, once granted, licensed products are closely monitored for the occurrence of suspected adverse effects. The safety of herbal medicinal products is of particular importance as the majority of these products is self-prescribed and is used to treat minor and often chronic conditions.

The extensive traditional use of plants as medicines has enabled those medicines with acute and obvious signs of toxicity to be well recognised and their use avoided. However, the premise that traditional use of a plant for perhaps many hundreds of years establishes its safety does not necessarily hold true.[22, 126, 127] The more subtle and chronic forms of toxicity, such as carcinogenicity, mutagenicity and hepatotoxicity, may well have been overlooked by previous generations and it is these types of toxicities that are of most concern when assessing the safety of herbal remedies.

A UK Medical Toxicology Unit conducted a study of potentially serious adverse reactions associated with exposure to traditional medicines and food supplements during 1991 to 1995.[128] Of 1297 enquiries from healthcare professionals, a total of 785 cases were identified as possible (n = 738), probable (n = 35) or confirmed (n = 12) cases of poisoning caused by traditional medicines or food supplements. The report concluded that the overall risk to public health from these types of products was low. However, clusters of cases were identified that gave cause for concern. Twenty-one cases of liver toxicity, including two deaths, were associated with the use of traditional Chinese medicines, although no causative agent was identified.

Potential hepatotoxicity associated with herbal medicines has been discussed for some time.[129, 130] Hepatotoxicity has been reported with a number of herbal medicines (*see* monographs on Black Cohosh, Chaparral, Comfrey, Ephedra, Kava). *Teucrium* species (*see* Scullcap) have also been implicated in hepatotoxicity. Following reports of serious cases of liver toxicity associated with the use of *Piper methysticum* (*see* Kava), *P. methysticum* has been prohibited in unlicensed medicinal products in the UK since January 2003.[58]

At the time of writing, MHRA was aware of 79 cases of liver damage associated with the consumption of kava that have been reported worldwide.[90] Cases of hepatotoxicity associated with the use of Black Cohosh have also been reported (*see* Black Cohosh).[90]

Intrinsically toxic constituents of herbal ingredients

Limited toxicological data are available on medicinal plants. However, there exists a considerable overlap between those herbs used for medicinal purposes and those used for cosmetic or culinary purposes, for which a significant body of information exists. For many culinary herbs used in herbal remedies, there is

no reason to doubt their safety providing the intended dose and route of administration is in line with their food use. When intended for use in larger therapeutic doses the safety of culinary herbs requires re-evaluation.

Culinary herbs Some culinary herbs contain potentially toxic constituents. The safe use of these herbs is ensured by limiting the amount of constituent permitted in a food product to a concentration not considered to represent a health hazard.

Apiole The irritant principle present in the volatile oil of parsley is held to be responsible for the abortifacient action.[131] Apiole is also hepatotoxic and liver damage has been documented as a result of excessive ingestion of parsley, far exceeding normal dietary consumption, over a prolonged period (*see* Parsley).[131]

β-*Asarone* Calamus rhizome oil contains β-asarone as the major component, which has been shown to be carcinogenic in animal studies.[131] Many other culinary herbs contain low levels of β-asarone in their volatile oils and therefore the level of β-asarone permitted in foods as a flavouring is restricted. The EMEA HMPC has concluded that in view of the toxicity of α-and β-asarone, their concentration in herbal medicinal products should be reduced to minimum and diploid varieties should always be preferred. In analogy with the food regulation (limitation of the intake of β-asarone from food and alcoholic beverages), a limit of exposure from herbal medicinal products of approximately 115 µg/day, i.e. about 2 µg/kg body weight/day could be accepted temporarily until a full benefit–risk assessment has been carried out.[132]

Estragole (Methylchavicol) Estragole is a constituent of many culinary herbs but is a major component of the oils of tarragon, fennel, sweet basil and chervil. Estragole has been reported to be carcinogenic in animals.[131] The level of estragole permitted in food products as a flavouring is restricted. The EMEA HMPC has concluded that the present exposure to estragole resulting from consumption of herbal medicinal products (short time use in adults at recommended posology) does not pose a significant cancer risk. Nevertheless, further studies are needed to define both the nature and implications of the dose–response curve in rats at low levels of exposure to estragole. In the meantime exposure of estragole to sensitive groups such as young children, pregnant and breastfeeding women should be minimised. Toxicological assessment of preparations for topical and external use needs further investigation because data on absorption through the skin are missing.[133]

Safrole Animal studies involving safrole, the major component of sassafras oil, have shown it to be hepatotoxic and carcinogenic.[131] The permitted level of safrole as a flavouring in foods is 0.1 mg/kg.

Methyleugenol Methyleugenol is a constituent of many culinary herbs and is present in small amounts in cassia bark oil and clove oil (*see* Cassia, Clove). Chronic toxicity data on methyleugenol show the compound to be a genotoxic carcinogen. The EMEA HMPC has concluded that the present exposure to methyleugenol resulting from consumption of herbal medicinal products (short time use in adults at recommended posology) does not pose a significant cancer risk. Nevertheless, further studies are needed to define both the nature and implications of the dose–response curve in rats at low levels of exposure to methyleugenol. In the meantime, exposure of sensitive groups, such as young children, pregnant and breastfeeding women, to methyleugenol should be minimised. Toxicological assessment of preparations for topical and external use needs further investigation because data on absorption through the skin are missing.[134]

Other intrinsically toxic constituents *Aristolochic acids* are reported to occur only in the Aristolochiaceae family. They have been reported in *Aristolochia* species, and appear to occur throughout the plant in the roots, stem, herb and fruit. The aristolochic acids are a series of substituted nitrophenanthrene carboxylic acids. The main constituents are 3,4-methylene-dioxy-8-methoxy-10-nitrophenanthrene-1-carboxylic acid. Low concentrations of aristolochic acids have been reported in *Asarum* species, another member of the Aristolochiaceae family. Aristolochic acids have been shown to be nephrotoxic, carcinogenic and mutagenic.[135]

Pyrrolizidine alkaloids are present in a number of plant genera, notably *Crotalaria*, *Heliotropium* and *Senecio*. Many of these plants have been used in African, Caribbean and South American countries as food sources and as medicinal 'bush teas'. Hepatotoxicity associated with their consumption is well documented and has been attributed to the pyrrolizidine alkaloid constituents.[136, 137] Pyrrolizidine alkaloids can be divided into two categories based on their structure, namely those with an unsaturated nucleus (toxic) and those with a saturated nucleus (considered to be non-toxic).

Several herbs currently used in herbal remedies contain pyrrolizidines; they include liferoot, borage, comfrey, coltsfoot and echinacea (*see* individual monographs).

In addition to preclinical data, cases of human hepatotoxicity associated with the ingestion of comfrey have been documented (*see* Comfrey). The concentrations of pyrrolizidine alkaloids present in borage and coltsfoot are thought to be too low to be of clinical significance, although the dangers associated with long-term low-dose exposure are unclear. The use of borage oil as a source of gamma-linolenic acid and as an alternative to evening primrose oil is currently very popular. The pyrrolizidine alkaloids identified in echinacea to date have been of the non-toxic saturated type. In 2002, MHRA raised concerns about a TCM product known as Qianbai Biyan Pian available on the UK market containing *Senecio scandens* which is reported to contain the unsaturated pyrrolizidine alkaloids, senecionine and seneciphylline.[90]

Benzophenanthridine alkaloids are present in bloodroot and in prickly ash. Although some of these alkaloids have exhibited cytotoxic properties in animal studies, their toxicity to humans has been refuted (*see* Bloodroot).

Lectins are plant proteins that possess haemagglutinating and potent mitogenic properties. Both mistletoe and pokeroot contain lectins. Systemic exposure to pokeroot has resulted in haematological aberrations. Mistletoe lectins may also inhibit protein synthesis.[138] (*see* Mistletoe and Pokeroot).

Viscotoxins, constituents of mistletoe, are low molecular weight proteins which possess cytotoxic and cardiotoxic properties.[138] For many years, mistletoe preparations have been used in Europe as cancer treatments. Clinical trials carried out with Iscador, a product produced from the naturally fermented plant juice of mistletoe, have concluded that Iscador may exhibit some weak antitumour effects but should only be used alongside conventional therapy in the long-term treatment of cancer.

Lignans. Hepatotoxic reactions reported for chaparral have been associated with the lignan constituents (*see* Chaparral).

Table 1 Examples of adverse effects that may occur with herbal ingredients

Potential adverse effect	Constituent/Herbal ingredient
Allergic (*see* Appendix 2, Table 11)	
Hypersensitive	Sesquiterpene lactones: arnica, chamomile, feverfew, yarrow
Phototoxic	Furanocoumarins: angelica, celery, wild carrot
Immune	Canavanine: alfalfa
Cardiac (*see* Appendix 2, Table 2)	Cardiac glycosides: pleurisy root, squill
Endocrine	
Hypoglycaemic (*see* Appendix 2, Table 8)	Alfalfa, fenugreek
Hyperthyroid	Iodine: fucus
Hormonal (*see* Appendix 2, Table 9)	
Mineralocorticoid	Triterpenoids: liquorice
Oestrogenic; Anti-androgen	Isoflavonoids: alfalfa; red clover Saponins: ginseng, saw palmetto
Irritant (*see* Appendix 2, Table 12)	
Gastrointestinal	Numerous compounds including anthraquinones (purgative), capsaicinoids, diterpenes, saponins, terpene-rich volatile oils
Renal	Aescin: horse-chestnut; terpene-rich volatile oils
Toxic	
Hepatotoxic/carcinogenic	Pyrrolizidine alkaloids: comfrey, liferoot; β-asarone: calamus; lignans: chaparral; safrole: sassafras; hepatotoxic constituents unconfirmed: black cohosh, kava
Mitogenic	Proteins: mistletoe, pokeroot
Cyanide poisoning	Cyanogenetic glycosides: apricot
Convulsant	Camphor/thujone-rich volatile oils

Saponins. Pokeroot also contains irritant saponins which have produced severe gastrointestinal irritation involving intense abdominal cramping and haematemesis. Systemic exposure to these saponins has resulted in hypotension and tachycardia. In May 1979, the US Herb Trade Association requested that all its members should stop selling pokeroot as a herbal beverage or food because of its toxicity.[139]

Diterpenes. The irritant properties of many diterpenes are well documented and queen's delight contains diterpene esters which are extremely irritant to all mucosal surfaces (*see* Queen's Delight).

Cyanogenetic glycosides are present in the kernels of a number of fruits including apricot, bitter almond, cherry, pear and plum seeds. Gastric hydrolysis of these compounds following oral ingestion results in the release of hydrogen cyanide (HCN), which is rapidly absorbed from the upper gastrointestinal tract and which can lead to respiratory failure. It has been estimated that oral doses of 50 mg of HCN, equivalent to about 50–60 apricot kernels, can be fatal[140] (*see* Apricot). However, variation in cyanogenetic glycoside content of the kernels could reduce or increase the number required for a fatal reaction. In the early 1980s a substance called amygdalin was promoted as a 'natural' non-toxic cure for cancer. Amygdalin is a cyanogenetic glycoside that is also referred to as laetrile and 'vitamin B_{17}'. Two near-fatal episodes of HCN poisoning were recorded in which the patients had consumed apricot kernels as an alternative source of amygdalin, due to the poor availability of laetrile. Scientific research did not support the claims made for laetrile, although a small number of anecdotal reports suggested that laetrile may have some slight anticancer activity. As a result, legislation drawn up in 1984[141] restricted the availability of cyanogenetic substances so that amygdalin can only be administered under medical supervision.

Furanocoumarins are found predominantly in the families Umbelliferae (e.g. parsley, celery), Rutaceae (e.g. bergamot, *Citrus* species), Moraceae and Leguminosae. The furanocoumarins occur as linear and branched forms: the most commonly reported linear furanocoumarins are 8-methoxypsoralen, 5-methoxypsoralen (bergapten) and psoralen. The furanocoumarins are phototoxic. Severe phototoxic reactions have been reported in humans following the use of bergamot oil in topical preparations. Severe phototoxic burns have been reported in a Swedish patient following a visit to a suntan parlour after ingestion of a large quantity of celery soup.[142] In the UK, a patient developed severe phototoxicity during oral photochemotherapy with psoralen and ultraviolet A (PUVA) after eating a large quantity of soup made from celery, parsley and parsnip.[143] The authors highlighted the potential hazards of eating foods containing psoralens during PUVA therapy. In the UK, the MCA received two reports describing severe skin burns in patients who had been treated with TCM preparations derived from *Psoralea corylifolia* fruit.[144]

Volatile oils. *See* Precautions in specific patient groups, Pregnant/breastfeeding mothers, below.

Herbal ingredients that may cause adverse effects

Examples of adverse effects that have been documented in humans or animals for the herbal ingredients described in the monographs are summarised in Table 1. These adverse effects include allergic,