Phytopharmacy

an Evidence-Based Guide to Herbal Medicinal Products

Sarah E Edwards • Inês da Costa Rocha
Elizabeth M Williamson • Michael Heinrich

WILEY Blackwell

Phytopharmacy

Phytopharmacy

An evidence-based guide to herbal medicinal products

Sarah E. Edwards
Inês da Costa Rocha
Elizabeth M. Williamson
Michael Heinrich

WILEY Blackwell

Registered office: John Wiley & Sons, Ltd, The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, UK
Editorial offices: 9600 Garsington Road, Oxford, OX4 2DQ, UK
The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, UK
111 River Street, Hoboken, NJ 07030-5774, USA

For details of our global editorial offices, for customer services and for information about how to apply for permission to reuse the copyright material in this book please see our website at www.wiley.com/wiley-blackwell.

Library of Congress Cataloging-in-Publication Data

Edwards, Sarah E., author.
Phytopharmacy : an evidence-based guide to herbal medical products / Sarah E. Edwards, Michael Heinrich, Ines Rocha, Elizabeth M. Williamson.
p. ; cm.
Includes bibliographical references.
ISBN 978-1-118-54356-6 (pbk.)
I. Heinrich, Michael, 1957 July 4-, author. II. Rocha, Ines, author. III. Williamson, Elizabeth M., author. IV. Title.
[DNLM: 1. Plant Preparations–pharmacology. 2. Evidence-Based Practice. 3. Phytotherapy. 4. Plant Preparations–therapeutic use. QV 766]
RM666.H33
615.3′21–dc23

2014033180

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

Wiley also publishes its books in a variety of electronic formats. Some content that appears in print may not be available in electronic books.

The cover image is of *Ginkgo biloba* L., which is used in the treatment of diseases associated with milder forms of memory disorders and to enhance cognition. Photograph courtesy of Michael Heinrich

Typeset in 9/10pt TimesLTStd by Laserwords Private Limited, Chennai, India

1 2015

Contents

Preface

The increasing use of herbal medicines and botanical food supplements, either taken alone or in addition to orthodox treatment, presents a conundrum for the conventionally trained healthcare professional. Patients nowadays often prefer – and are encouraged – to take some responsibility for their own health and treatment options, and frequently purchase herbal medicines/botanical food supplements that they have read about in the popular press. This may be in an effort to generally improve their health or 'boost the immune system' or, as they see it, for the adjunctive treatment of specific disorders, regardless of whether expert advice was sought. *Doctors* may be asked whether it is safe for patients to take these products alongside their prescribed medicines; *pharmacists* who dispense those prescribed medicines and also sell herbal products, are asked which they can recommend; and *nurses* who look after patients on a long-term practical basis are asked for advice on all kinds of health issues. Numerous studies have shown that these practitioners consider their knowledge in the area of herbal medicines to be generally weak, especially regarding the potential therapeutic benefits, adverse effects, or possible interactions with prescribed or over-the-counter medicines. In addition to the healthcare professional, many patients are well-informed about their own health issues and medication (the 'expert patient') and are quite capable of making safe decisions about their own use of herbal medicines if they have access to the relevant information.

In the European Union, many herbal medicines are now regulated as medicines under the Traditional Herbal Medicinal Products Directive (http://www.mhra.gov.uk/Howweregulate/Medicines/Herbalmedicinesregulation/), placing new responsibilities on healthcare professionals. These traditional herbal registered (THR) products guarantee safety and quality, but in place of clinical trials (which may not have been carried out for economic reasons), a documented history of use in Europe is used instead. Herbal substances that are major ingredients in UK THR products are indicated as such in the presented monographs.

This book provides relevant information in a practical and useful way for the busy pharmacist, nurse or doctor, as well as the 'expert patient'. It gives a summary of the properties and uses of the most important herbal medicinal products and botanical food supplements, including an assessment of the available scientific evidence. It has been compiled on the premise that healthcare professionals (regardless of their own personal opinions) recognise patient and consumer demands for these products and need to be knowledgeable about them. The evidence available, both clinical and pre-clinical, is summarised to enable an evidence-based decision to be made as to whether the use of a particular nutritional or herbal medicinal product is advisable and safe.

We gratefully acknowledge funding through the UK government's matched funding scheme provided by Fa. Schwabe Pharmaceuticals and Bionorica (Germany) to

the School of Pharmacy, Univ. London (M.Heinrich), which funded SE's and ICR's positions. The donors had no influence on the writing of the book.

Sarah Edwards,
UCL School of Pharmacy & Royal Botanic Gardens, Kew

Inês da Costa Rocha,
UCL School of Pharmacy

Elizabeth M. Williamson,
School of Pharmacy, University of Reading

Michael Heinrich,
UCL School of Pharmacy

Introduction

A Handbook of Herbal Medicines for the Practitioner and the Expert Patient

Herbal medicines are used increasingly in the United Kingdom, either alone or in addition to conventional treatment, which presents difficulties for the conventionally trained pharmacist, doctor, nurse, dentist, and so on. Herbal and nutritional products tend to be ignored by these practitioners, despite the fact that they are also used by some of these same professionals! It is important to be able to advise patients on the safe use of such products, including any possible interactions with prescribed or over-the-counter (OTC) medicines. However, although based on studies that are sparse, small and/or restricted to a particular setting, it can be concluded that generally health care professionals feel that their knowledge in this area is weak.

Doctors tend to know little about any aspect of herbal medicines, and often do not ask the patient if they are taking any (e.g. Lisk 2012), whereas pharmacists are more likely to answer correctly about the use of herbs, rather than about cautions, adverse effects, and interactions (e.g. Cuzzolin and Benoni 2009). Nurses also feel that their knowledge of herbal medicines is lacking (e.g. Temple et al. 2005) and in all surveys reported, respondents felt that health care professionals should know more, and that they themselves would benefit from training in this area. This book is an attempt to redress that lack of knowledge and provide useful practical information for the busy practitioner. It is intended to provide an overview of the most important medicinal and health food plants and products commonly used in the British Isles, including an assessment of the scientific evidence available for these 'herbal medicines'. It is based on the premise that health care professionals must recognise patient and consumer demands for these products, regardless of their own personal opinions, and therefore be knowledgeable about them - especially as many are now regulated as medicines.

A recent concept in medical treatment is that of the 'expert patient': someone who usually has a long-term health condition but who is able to take more control over their health by understanding and managing the condition, leading to an improved quality of life. Many patients who wish to take herbal and nutritional supplements do their own research, often over the Internet, and so are at risk of receiving biased information by vested interests, or politically or philosophically motivated groups. The information given in this book is taken only from peer-reviewed resources and written in language that the expert patient can normally understand, in an attempt to provide an informative and safe resource for the patient, as well as the practitioner.

The introductory chapters are based on a series of articles by the authors in the *Pharmaceutical Journal* in 2012: 288:565-566; 288:627-628; 288: 685-686; 289:161-162; 289: 270-271.

Phytopharmacy: An evidence-based guide to herbal medicinal products, First Edition.
Sarah E. Edwards, Inês da Costa Rocha, Elizabeth M. Williamson and Michael Heinrich.

Definitions, the market and the legal position

What are herbal medicines and who uses them? Many people in the United Kingdom regularly use complementary and alternative medicine (CAM), either alone or in addition to conventional treatment. A recent systematic review has concluded that the average 1-year prevalence of use of CAM in the United Kingdom is >40% and the average lifetime prevalence >50%, with the most popular type being herbal medicine, at 29.5% (Posadzki et al. 2013). In 2003–2004, £3.25 bn was spent on herbal treatments alone in Western Europe (WHO 2008), and the global herbal supplements market is forecast to reach about £70 bn by the year 2017 (Global Industry Analysts 2013). These products are not only used by the 'worried well': a UK study found that 20% of cancer patients have used herbal medicines (Damery et al. 2011) and elsewhere, usage is even higher (see Williamson et al. 2013 for more details). Despite this, there generally is a lack of understanding of what herbal medicines actually are – or are not (IPSOS-MORI 2008).

Historically, plants have yielded many of our most important drugs, including morphine, taxol and digoxin, which are highly potent natural product – but not 'herbal' – medicines. Isolated compounds from plants are, in effect, identical as far as formulation, quality control and regulatory issues are concerned, to synthetic drugs or 'single chemical entities'. Herbal medicines are different in that they are prepared from plant material, but with little or no chemical fractionation and thus contain a wide range of natural compounds, some of which are pharmacologically active, and some of which are not. They can be licensed in the same way as 'conventional' medicines (e.g. *Senna alexandrina* Mill. tablets, ispaghula husk preparations, capsaicin cream), and even regulated as controlled drugs (e.g. cannabis oromucosal spray; MHRA 2010) - but if so, they are not usually considered to be 'herbal' medicines. Most frequently, botanical 'drugs' are available as food supplements and herbal medicines (e.g. rhodiola and black cohosh preparations), and can be purchased from health food and general stores, as well as pharmacies.

CAM encompasses a wide range of therapies, based generally on philosophical and cultural traditions rather than clinical evidence, and may or may not have been investigated scientifically. Some herbal medicinal products (HMPs) are fully licensed (and therefore not part of CAM), whereas others are registered under the Traditional Herbal Registration (THR) scheme on the basis of traditional use only (see later). The licensed products, and even many of the THRs, have been demonstrated to be pharmacologically active medicines and should be treated as such by health care professionals, with all of the issues that entails. The regulatory framework of HMPs has, however, been interpreted in a variety of ways, and consequently some products remain unlicensed and are classified as 'food supplements'.

UK regulation is largely based on European Union legislation, Directive 2001/83/EC, the European Traditional Herbal Medicinal Products Directive (THMPD) and the 1968 Medicines Act (Heinrich et al. 2012). Under this legislation, manufacturers of all products (including herbal remedies) classified as medicinal products must hold a marketing authorisation (MA, or product licence, PL) for that product, unless it satisfies the criteria for exemption from the requirement for an MA. In essence, medicinal products are defined by presentation (the purpose of the product), *or* by function (the actual effect of the product). All new chemical entities, including isolated constituents from plant and other natural sources, must have MAs for those products, based on the full dossier of chemical, pharmaceutical, pharmacological, toxicological and clinical data.

The legal position of herbal medicines in the United Kingdom: Herbal medicines are classed as medicinal products by the MHRA (2012a). While globally between

40,000 and 50,000 plant species are used for medicinal purposes in both traditional and modern medical systems (Heywood 2011), only a few hundred are used more widely in the United Kingdom, other European countries, North America or Australia.

Herbal products are available on the UK market as:

- Licensed (herbal) medicines
- Traditional herbal medicinal products registered under the THMPD
- Herbal medicines exempt from licensing, which comprise three groups:
  a) Unlicensed herbal medicines supplied (and often made) by a practitioner following a one-to-one consultation
  b) Manufactured or imported herbal products for individual patients commissioned from a third party ('specials')
  c) Unprocessed, that is, dried and cut herbal medicines (produced by subjecting a plant or mixture of plants to drying, crushing, cutting or a simple process of extraction)
- Medical devices, that is, products used to diagnose, prevent, or treat disease, but *without* chemical effects on the body
- Products sold as food or dietary supplements, often over the Internet
- Prescription-only medicines (POMs): potentially hazardous plants may only be dispensed by order of a prescription by a registered doctor.
- Pharmacy-only medicines (P), supplied by a registered pharmacist; these may be subject to restrictions of dose (but not duration of treatment) and/or route of administration.

Terminology used for herbal medicines: In addition to '*herbal medicines*', the term '*herbal medicinal products*' is also used, and highlights the commercial nature of these preparations. Less commonly, they may be called '*phytopharmaceuticals*', '*phytomedicines*', or even '*traditional medicines*'. In the United States, they are often referred to as '*botanicals*'; but in the United Kingdom, that also includes nutritional and cosmetic products. Similarly, a range of terms is also applied to foods with acclaimed health benefits: '*food supplements*', '*nutraceuticals*', '*health foods*' or '*medicinal foods*'. In this book, we use the term '*herbal medicines*' or '*herbal medicinal products*' *(HMPs)* to describe those which have a clearly defined medicinal use, and '*food supplements*' for those which are derived from foods and intended to supplement the diet or maintain health, rather than treat disease.

The production of herbal medicines: From a pharmaceutical perspective, herbal medicines may be extracts (usually aqueous, ethanolic or hydroalcoholic) or unprocessed (but usually powdered) dried plant material. 'Herbal drugs' are products that are either:

- derived from a plant: it may be the whole plant, or part of the plant such as the leaf, fruit, root, and so on, and prepared by simply drying and packaging (e.g. as a tea bag);
- obtained from a plant, but no longer retaining any recognisable structure of the plant: they still contain a complex mixture of compounds (e.g. essential oils, resins).

The chemical composition of individual plants is influenced by a combination of genetic and environmental factors, including soil, weather, season or time of day harvested, and use of any pesticides, herbicides and fertilisers. This has been demonstrated in various strains of *Sedum roseum* (better known by its synonym

name, *Rhodiola rosea*) which were moved geographically and also grown under varying conditions (Peschel et al. 2013). Processing and extraction procedures affect the final chemical composition of HMPs, and also explain why the chemical profile of two HMPs derived from the same plant species may differ considerably. The variation is significant because not all constituents make an equal contribution to the pharmacological effects of the herb. Herbs used for registered HMPs are either grown/produced under controlled (cultivated) agricultural conditions or wild harvested in compliance with Good Agricultural and Collection Practice (GACP), providing a high level of product quality, which is intrinsically linked with safety.

The next key step in the production of HMPs is the processing, including harvesting, of the relevant plant part. The processing (drying, cutting, storage, packaging and transport, etc.) of registered products must be in compliance with Good Manufacturing Practice (GMP). Human error and/or unscrupulous operators also influence the quality of the raw material. Accidental or intentional botanical substitution are far more likely to occur with unregistered products that don't comply with GMP, and the intentional adulteration with conventional drugs (e.g. corticosteroids) and contamination with microorganisms and pesticides continues to be of concern. An important benefit of registration under THMPD is the safeguarding of patients' health by implementing a number of stringent manufacturing and quality control requirements. There is therefore an ethical argument that health care professionals should only recommend registered or licensed products.

Specific extraction and processing techniques are available in both the British and European Pharmacopoeia (BP, Ph Eur) for processing crude plant material. These are tightly controlled by European and national legislation and the monographs provide legally binding quality assurance procedures for products available on the British market. The variability in content and concentrations of constituents of the plant material, together with the range of extraction techniques and processing steps used by different manufacturers, results in a marked variability in the content and quality of all herbal products. Both raw and processed materials therefore require monitoring in order to produce HMPs of consistent quality and to ensure bioequivalence (Loew and Kaszkin 2002). For registration under the THMPD, the applicant has to provide details about the production, processing, extraction and formulation process, as well as on the composition of the medicine, the dose per unit, and the daily dose.

The question of quality assurance is also linked to the concept of 'standardisation'. Although relatively new for HMPs, it is essential to ensure that patients are provided with *consistent,* high-quality, herbal products. Standardisation is only possible where the active constituents are known (which is not the case for many HMPs) and can be defined as the requirement for *a specified amount or range of one or several pharmacologically active compounds, or groups of compounds, in the extract*. Reproducibility of the chemical constituents in HMPs prevents accidental overdosing due to batch-to-batch variation as well as under-dosing, and therefore contributes to efficacy. Unfortunately, the term 'standardisation' is often misunderstood, if not misused, in herbal medicine promotion – but it is easy to comprehend if compared to blending coffee or even whisky, to make the consistent and familiar product that the customer expects! If the active constituents are not known, the extract cannot be standardised, although one or more 'marker' compounds characteristic of the botanical drug can be used to characterise the HMP chemically (Heinrich et al. 2012).

Quality issues for registered/licensed HMPs – a checklist of key parameters:

- Harvesting/collection of plants using GACP
- Full botanical authentication
- Test for contaminants (pesticide, herbicide residues; heavy metals; microbial contamination)
- Extraction methodology (quality assurance)
- Standardised extracts (active constituents (single or groups) are known)
- Quantified extracts (known therapeutic or pharmacological activity)

Combination effects and their importance: Single compounds that are derived and/or purified from plants are not HMPs and do not exhibit combination effects. Herbal medicines, however, even when prepared from only one plant, contain a large number of phytochemicals, rather than a single pharmacologically active substance. A principal tenet of herbal medicine is that this results in a unique activity profile, in which several compounds act on each other, either moderating, opposing, or enhancing an effect. An enhancement may be an '*additive*' or '*synergistic*' action, whereby the combination of constituents is greater than would have been expected from the sum of individual contributions. There is some evidence for this: in the case of *Ginkgo biloba* L., synergy in inhibiting platelet aggregation has been shown for ginkgolides, using the isobole method, and other components of cannabis are seen to enhance the activity of the CB1 agonist Δ-9 tetrahydrocannabinol in the extract (Williamson 2001). '*Antagonism*' is when the effect of a compound is inhibited by the presence of another, but this may of course be beneficial if the particular effect is unwanted. The term '*polyvalence*' is now often used to describe the full range of biological activities that contribute to the overall effects, and includes multi-target and well as multi-component effects (Wagner and Ulrich-Merzenich 2009). Polyvalence can also be shown by St. John's wort (*Hypericum perforatum* L.), used to treat mild-to-moderate depression, which contains a variety of compounds acting in different ways. For example, hyperforin inhibits serotonin reuptake, whereas hypericin inhibits binding to some subtypes of dopamine receptors, and the flavonoids also contribute to the activity (Russo et al. 2014).

The 'one target, one disease' (or 'silver bullet') concept is increasingly considered inadequate in many clinical situations (Wermuth 2004) and polypharmacy is routine in conditions such as cancer, hypertension and HIV infection. The use of multiple drugs increases the risk of adverse effects and drug interactions, and while HMPs and food supplements are generally not included in definitions of polypharmacy, they can also increase the risk of drug interactions, although a great deal of speculation and exaggeration surrounds this issue (Williamson et al. 2013).

Traditional Herbal Registration and why it is necessary: The Traditional Herbal Medicinal Products Directive stipulates that only *registered* herbal products may be sold as OTC medicines. THR medicines have known quality and safety, and documented traditional use. Only limited therapeutic claims can be made, and their use is only for minor self-limiting conditions. They may be administered via any route of administration (topical, oral, etc.) except for injectables, which are always POMs. They must be sold with a patient information leaflet (PIL) and can be identified by a THR number. They may also display the certification mark see Fig I.1 (which is not compulsory) on the packaging.

The implementation of the THMPD has resolved a number of safety issues surrounding the production of unregulated HMPs, by ensuring consistent quality

Figure 1 Traditional Herbal Registration certification mark

based on good manufacturing, agricultural and/or collection practices. The aim is to reduce the risk of problems caused by:

- contamination (e.g. with heavy metals, pesticides, insects or moulds);
- substitution (e.g. with other plant species, which may be toxic or ineffective)
- adulteration (both accidental and deliberate: this may be with other plant parts of the correct plant, such as stems and fruits in a leaf drug, or with other – usually inferior and cheaper – species, or with synthetic drugs such as corticosteroids).

A few potentially dangerous medicinal plants remain restricted to use as POMs. These include *Digitalis*, *Strychnos* and *Aconitum* species, with maximum doses and/or route of administration specified, but, in fact, are rarely found in practice in the United Kingdom. Some other herbal ingredients are prohibited, including *Aristolochia* species which are highly nephrotoxic (Heinrich et al. 2009).

Patients who use unlicensed herbal products have no guarantee that these comply with any regulations, or any definition of good practice, and so may be exposing themselves to risk. The MHRA's Yellow Card Scheme for pharmacovigilance applies to all *registered and licensed HMPs* in addition to conventional medicines, and should be used where there is concern that an adverse event or interaction has occurred as a result of their use.

In a few cases, a product may actually hold a product licence under the 'Well Established Use Directive'. This is where an HMP is supported by sufficient safety and efficacy data and consequently has a well-established medicinal use rather than just being based on 'traditional use'. It is a licensing route more commonly used in continental Europe than in the United Kingdom.

The importance of using THR products is very well illustrated by the case of butterbur (*Petasites hybridus*), which is used traditionally for migraine, asthma and hay fever. Products containing this herb have been linked to 40 cases of liver toxicity, including two cases of liver failure requiring transplantation. This plant is known to contain hepatotoxic pyrrolizidine alkaloids (PAs), but what is of real concern is that these cases involved the use of butterbur-containing products where the PAs had been removed, indicating that other constituents (possibly sesquiterpenes) were responsible for the toxicity. Butterbur is not found in any THRs registered in the United Kingdom but is an ingredient in a number of herbal products sold as food supplements (MHRA 2012c).

Herbal medicines as 'food supplements': A vast number of medicinal plants are also used as foods or in cosmetic preparations. The MHRA is responsible for classifying which herbal products are primarily medicines, and, therefore, fall within the remit of the THMPD, whereas those classified as 'food supplements' must comply with regulations set out by the Department of Health (DH 2011). Food supplements may be almost indiscernible from HMPs in terms of physiological effects (in fact,

the same herb may be sold as both a food supplement and an HMP), but they may not be sold with any therapeutic claims. Like HMPs, food supplements have the potential to interact with other medications; for example, garlic and cranberry may increase the risk of bleeding associated with antiplatelet or anticoagulant agents such as aspirin and warfarin (Williamson et al. 2013).

Herbal medicines as 'medical devices': In rare cases, a herbal product may be registered as a 'medical device'. For example, a 'fibre complex' from stems of the prickly pear cactus (*Opuntia ficus-indica*), has been registered as a medical device for weight loss. Since a number of adverse drug reactions have been reported for it (MHRA 2012b), this product, and the concept in general, remains controversial.

In summary, *there is a regulatory framework available for the control of the quality of herbal medicines, and for ethical reasons, health care professionals should only recommend registered or licensed products* (assuming they are available, of course). After all, no health care professional should prescribe, dispense or administer a product if they have no guarantee that it even contains what it says on the label.

Information given in this book is not a substitute for medical advice and no responsibility can be taken by the authors for adverse reactions.

References

Cuzzolin L, Benoni G. (2009) Attitudes and knowledge toward natural products safety in the pharmacy setting: an Italian study. *Phytotherapy Research.* 23(7) 1018–1023.

Damery S, Gratus C, Grieve R, Warmington S, Jones J, Routledge P, Greenfield S, Dowswell G, Sherriff J, Wilson S. (2011) The use of herbal medicines by people with cancer: a cross-sectional survey. *British Journal of Cancer* 104: 927–933.

Department of Health, UK. (2011) Food supplements - Summary information on legislation relating to the sale of food supplements, https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/204303/Supplements_Summary__Jan_2012__DH_FINAL.doc.pdf (accessed July 2013).

Global Industry Analysts. (2013). Herbal Supplements and Remedies: A Global Strategic Business Report. http://www.companiesandmarkets.com/Market/Consumer-Goods/Market-Research/Herbal-Supplements-and-Remedies-A-Global-Strategic-Business-Report/RPT907407 (accessed July 2013).

Heinrich M, Barnes J, Gibbons S, Williamson EM. (2012) *Fundamentals of Pharmacognosy and Phytotherapy*. 2nd Edition. Churchill Livingston Elsevier, Edinburgh and London.

Heinrich M, Chan J, Wanke S, Neinhuis C, Simmonds MSJ. (2009) Local uses of *Aristolochia* species and content of Aristolochic acid 1 and 2 – a global assessment based on bibliographic sources. *Journal of Ethnopharmacology* 125(1): 108–144.

Heywood V. (2011) Ethnopharmacology, food production, nutrition and biodiversity conservation: towards a sustainable future for indigenous peoples. *Journal of Ethnopharmacology* 137(1): 1–15.

IPSOS – MORI 2008 *Public Perceptions of Herbal Medicines General Public Qualitative & Quantitative Research*. IPSOS-Mori, London, UK.

Lisk C. (2012) Food for thought: doctors' knowledge of herbal medicines needs to be better. *Acute Medicine* 11(3): 134–137.

Loew D, Kaszkin M. (2002) Approaching the problem of bioequivalence of herbal medicinal products. *Phytotherapy Research* 16(8): 705–711.

MHRA. (2010). Medicines and Healthcare products Regulatory Agency Public Assessment Report. Sativex Oromucosal Spray. http://www.mhra.gov.uk/home/groups/par/documents/websiteresources/con084961.pdf (accessed July 2013).

MHRA. (2012a). A guide to what is a medicinal product. MHRA Guidance Note No. 8. http://www.mhra.gov.uk/home/groups/is-lic/documents/publication/con007544.pdf (accessed July 2013).

MHRA. (2012b) Drug Analysis Print. *Opuntia ficus-indica*. http://www.mhra.gov.uk/home/groups/public/documents/sentineldocuments/dap_4869624197041.pdf (accessed July 2013).

MHRA. (2012c) Unlicensed butterbur (*Petasites hybridus*) herbal remedies http://www.mhra.gov.uk/home/groups/comms-ic/documents/websiteresources/con140851.pdf (accessed July 2013).

Peschel W, Prieto MJ, Karkour C, Williamson EM. (2013) Effect of provenance, plant part and processing on extract profiles from cultivated European *Rhodiola* for medicine use. *Phytochemistry* 86: 92–102.

Posadzki P, Watson LK, Alotaibi A, Ernst E. (2013) Prevalence of use of complementary and alternative medicine (CAM) by patients/consumers in the UK: systematic review of surveys. *Clinical Medicine* 13(2): 126–31.

Russo E, Scicchitano F, Whalley BJ, Mazzitello C, Ciriaco M, Esposito S, Patanè M, Upton R, Pugliese M, Chimirri S, Mammì M, Palleria C, De Sarro G. (2014) *Hypericum perforatum*: pharmacokinetic, mechanism of action, tolerability and clinical drug-drug interactions. *Phytotherapy Research* 28(5): 643–655.

Temple MD, Fagerlund K, Saewyc E. (2005) A national survey of certified registered nurse anesthetists' knowledge, beliefs, and assessment of herbal supplements in the anesthesia setting. *American Association of Nurse Anesthetists Journal* 73(5): 368–377.

Wagner H, Ulrich-Merzenich G. (2009) Synergy research: approaching a new generation of phytopharmaceuticals. *Phytomedicine* 16(2–3): 97–110.

Wermuth CG. (2004) Multitargeted drugs: the end of the "one-target-one-disease" philosophy? *Drug Discovery Today* 9(19): 826–827.

Williamson EM. (2001) Synergy and other interactions in phytomedicines. *Phytomedicine* 8(5): 401–440.

Williamson EM, Driver S, Baxter K. (Eds.) (2013) *Stockley's Herbal Medicines Interactions*. 2nd Edition. Pharmaceutical Press, London, UK.

WHO. (2008) *Traditional Medicine*. Fact Sheet No. 134. WHO, Geneva.

The Evidence Base for Herbal Medicines

Efficacy, clinical effectiveness and comparative effectiveness: The term 'efficacy' has a somewhat different definition according to context. In medicine, it is considered to be *the capacity for a health intervention to produce a therapeutic effect*; whereas within the discipline of pharmacology, it means the maximum response achievable from a drug.

To avoid confusion, the term 'clinical effectiveness' can be used to describe how well a medicine works in practice, as it encompasses both the biological effects of the constituents as well as any non-pharmacological influences (such as placebo or nocebo effects).

In recent years, the classical approach to evaluating medicines has been scrutinised from the perspective of how clinical studies can actually inform about treatment outcomes. For herbal medicines, 'comparative effectiveness' research has been proposed as a means of assessing their effectiveness in everyday practice settings, meaning the use of trials that compare 'real-world' situations rather than isolated interventions. Overall, this results in the capacity to inform specific clinical decisions (see Witt 2013 and references therein).

Comparative effectiveness research includes:

- the possibility of comparing two or more health interventions (a specific medication or therapy) to determine which option works best for which type of patient;
- the design of studies using 'typical patients' and in 'everyday' settings, that is, similar to those in which the intervention will be used.

The non-pharmacological functions of medicines are often overlooked, yet they play a significant role in eliciting the so-called 'meaning response', which refers to the 'physiological or psychological effects of meaning in the origins or treatment of illness', such as the production of endogenous opiates in response to an intervention. Placebo effects appear to be the result of a number of different mechanisms, including expectation, anxiety and reward, in addition to learning phenomena such as Pavlovian conditioning, and cognitive and social learning. With regard to traditional herbal medicines, the sociocultural aspects are even more likely to elicit a physiological response, in addition to any intrinsic pharmacological activity of the plant, since they often exist within religious and mythical traditions, creating a vivid associated meaning (Moerman and Jonas 2002).

The use of herbal medicines and similar products should therefore be considered within the context of their use, as this undoubtedly will have an impact on their clinical effectiveness. In traditional medicine, a healer may also use ritual and prayer along with herbal treatment, which may induce a meaning response, adding to the therapeutic effects of the plant extract. (This is not as far from modern medicine as

Phytopharmacy: An evidence-based guide to herbal medicinal products, First Edition.
Sarah E. Edwards, Inês da Costa Rocha, Elizabeth M. Williamson and Michael Heinrich.

might be supposed and most pharmacists have patients who only find a particular brand of drug to be effective: for example, 'only the blue tablets work on me'!) It is also essential to understand that the UK approach to herbal medicines is very cautious, and that some products, which are not considered to have evidence for clinical effectiveness, may be widely accepted in medical practice and as OTC products in other countries (e.g. see Schulz et al. 2004).

What evidence is available and how can it be interpreted? Evidence of clinical effectiveness is rated according to quality, with the highest levels of evidence ascribed to systematic reviews and meta-analyses of randomised controlled trials (RCTs). Key resources for such evidence include the Cochrane reviews, which are produced by an international collaboration of scientists. These reviews are globally recognised as '*the benchmark for high quality information about the effectiveness of health care*' and are freely available at http://www.cochrane.org/.

Figure 2 summarises the levels of evidence recognised today. This is largely a clinical perspective highlighting how detailed the clinical and pharmacological assessment has been, but of course it is intrinsically linked to the composition of a particular product and therefore to the production and processing of the herbal medicine. These levels of evidence are not as sharp as they appear in the diagram, and they are sometimes interpreted differently by the regulatory authorities of EU member states!

A criticism commonly levelled at HMPs is that for many of those on the market there is a lack of clinical data from good quality RCTs, usually, it is stated, due to limited funding. Although it is true that there is a paucity of data, Cochrane reviews do exist for a few herbal medicines. For example, a Cochrane review of RCTs on herbal medicine to treat low back pain, found that Devil's claw (*Harpagophytum procumbens* DC.) and white willow bark (*Salix alba* L.) seemed to reduce pain more than placebo in short-term trials, with the qualification that further trials were needed to clarify their equivalence against standard treatments in terms of efficacy, and that for long-term use there was no evidence that these substances are safe and useful (Gagnier et al. 2006). Another Cochrane review on St. John's

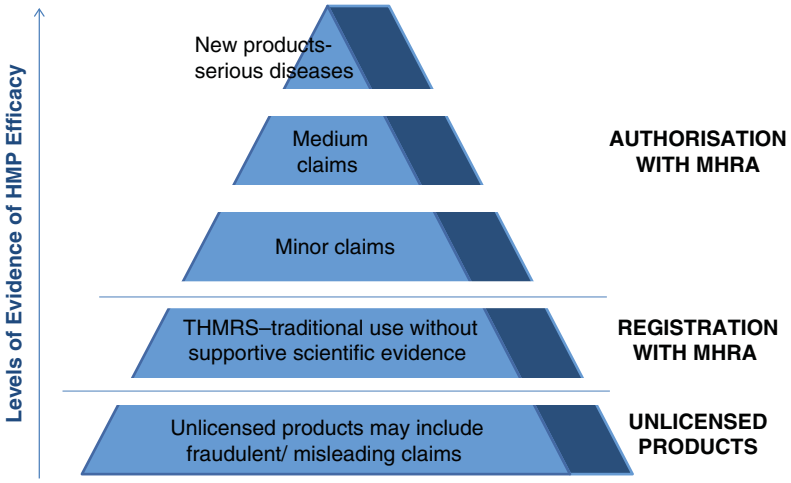

Figure 2 Levels of evidence (adapted from figure by Prof. Dr. W. Knoss, BfArM, Bonn, Germany)

wort (*Hypericum perforatum* L.), showed that it was equivalent to selective serotonin uptake inhibitors (Linde et al. 2008). Despite this, in the United Kingdom, health claims for all these drugs can only be based on 'traditional use'.

Due to the nature of herbal medicines, that is, their variability in phytochemical makeup according to genotype, plant part used, and environmental conditions, even well-designed clinical trials may potentially be flawed unless these factors are taken into consideration. A study of Echinacea, which showed no pharmacological effect beyond placebo for treating the common cold in children, was criticised because it used non-standardised pressed plant juice from aerial parts only, rather than standardised extracts from the entire plant (Firenzuoli and Gori 2004; Kim et al. 2004; Taylor et al. 2003). Furthermore, although Cochrane reviews are considered by many to be the gold standard for evaluating clinical effectiveness, in the case of herbal medicines, concerns have been raised. A study exploring the 11 most relevant Cochrane reviews on herbal medicine identified that frequently, the herbal medicines in the included studies had not been sufficiently well characterised. The plausibility of the medication for the specific indication needs to be considered in the light of the chemical composition and it has been suggested that the guidelines for preparing Cochrane reviews be revised for herbal products (Davidson et al. 2013).

Understanding the mechanisms of action responsible for the clinical effects of herbal products is challenging due to the presence of multiple constituents within one herbal ingredient, and thus pharmacokinetic/ pharmacodynamic data for these products are often unavailable. In Ayurvedic and traditional Chinese medicine (TCM) preparations, the complexity is compounded by the fact that each preparation usually contains multiple herbal (and sometimes non-herbal) components, each ingredient possibly containing a number of (as yet unknown) bioactive constituents. While pharmacological (and occasionally clinical) evidence for the properties of herbal extracts, mixtures and products is constantly being published, in journals such as the *Journal of Ethnopharmacology*, *Phytotherapy Research*, *Planta Medica*, *Fitoterapia* and *Phytomedicine*, there is a lack of a critical synthesis and applicability into everyday applications.

In this book we take a pragmatic approach and want to make clear that, while the level of evidence may be limited, these levels of evidence actually vary, in the manner shown in Figure 2. Note that this classification system is based on *available* evidence and should not be confused with clinical efficacy. We have defined five levels which highlight the level of evidence available for a specific botanical drug and the preparations derived from it.

Of course, 'lack of evidence for efficacy' is not the same 'as evidence for lack of efficacy', but from the perspective of the THMPD, the proven traditional use is the *only* relevant criterion (as well as the absence of toxicity reports) for registration, and we do not attempt to replace this classification. We do however highlight that different levels of evidence exist even within this group of HMPs.

In the Complementary and Alternative Medicine (CAM) sector, limited clinical evidence for herbal medicines is often not considered a serious problem by consumers (and often practitioners). It is assumed that a history of traditional use over many generations, without observed negative effects and in addition to being 'natural', implies that they are safe.

However, that implies that detailed knowledge of these products is available and that they have been produced using GACP, GMP and other Good Practice guidelines, which is often not the case, and it also depends hugely on what happens along the chain of supply from the grower to the buyer (Booker et al. 2012). The issue of quality has been discussed in more detail in the introduction.

Even with a long tradition of use for a particular herbal medicine, toxic effects may be delayed and a connection between cause and effect will not be made.

A well-known example is that of *Aristolochia,* a genus of plants used for perhaps thousands of years in traditional medical systems throughout the world. Awareness of the toxicity of *Aristolochia* only developed in the 1990s when a number of women in Belgium attending a slimming clinic developed kidney failure after being given a herbal medicine containing the herb *Aristolochia fangchi* (for the full story, see Heinrich et al. 2009). Today, despite a ban on this ingredient in most countries, cases of toxicity caused by the accidental or deliberate supply of products containing *Aristolochia* still occur, and the problem is exacerbated by the fact that other medicinal herbs have a similar appearance and similar Chinese common names.

There are other key concerns relating to the safety of use of TCM and Ayurvedic medicines, where the presence of high levels of heavy metals such as mercury, lead and arsenic have been found (MHRA 2013). Another complex example of toxicity is aconite (species of *Aconitum*), which is used in TCM for a wide range of indications, including many chronic conditions. The cardio- and neurotoxicity of this drug is potentially lethal, and the improper use of *Aconitum* in China, India, Japan and some other countries has led to cases of severe intoxication and death. According to claims made by some proponents of TCM, the tubers and roots can be detoxified by unique preparation methods, which are claimed to reduce the amount of toxic aconitine-type alkaloids present. While botanical drugs, which contain less than a threshold of aconitine, can be used medicinally in China, this position is not accepted in most Europe an countries, where aconite species may not be used under any circumstances (Singhuber et al. 2009). (In the United Kingdom, aconite may be found in licensed homeopathic remedies in which it is rigorously diluted. As an ingredient of an oral medicine its use is restricted and only available on prescription by a registered doctor or dentist.) TCM uses many toxic materials, especially in China (Liu et al. 2013). Despite this, the most commonly used TCM drugs in practice, in both China and the European Union, seem to be fairly safe. The most toxic drugs are used for serious diseases, a practice more likely in China (Williamson et al. 2013a). It is of course illegal to advertise non-licensed medicines for the treatment of conditions such as cancer, hypertension, and so on, in Europe.

Assessing the interaction potential of herbal medicines: Since the majority of HMPs are OTC medicines, it is of utmost importance that pharmacists, as well as manufacturers through patient information leaflets (PILs), raise awareness of the interaction potential and associated side effects of these products. Pharmacists in primary care encounter patients who take herbal medicines or supplements every day, and often sell HMPs in their stores, whereas pharmacists in secondary care should be aware that patients do bring their supplements into hospital with them, and sometimes continue to take them unbeknownst to the surgeon, anaesthetist, clinical pharmacists and nurses looking after them.

Patients should therefore be asked routinely about their use of herbal products, when dispensing medicines and taking a drug history on hospital admission, so that pharmacists can help the doctor and patient make a fully informed decision about their care. Special attention needs to be paid to long-term users and/or consumers of large amounts of HMPs, or patients who use many different medicinal products concomitantly, as they are more likely to suffer from adverse reactions. It is also rather worrying than many pregnant or nursing women take herbal medicines (Cuzzolin et al. 2011), and that these are also given to babies and children (Gottschling et al. 2013; Lim et al. 2011). Other groups at risk include the elderly, the malnourished or undernourished, as well as patients with serious medical conditions including heart disease, cancer, diabetes and asthma. As an example, patients with hypertension or congestive heart failure should not use *Ephedra*, often included in weight loss products, as it increases heart rate and blood pressure. *Ephedra* is legally restricted in

the United Kingdom, but can be bought easily over the Internet. The herb can also be supplied following a one-to-one consultation with a practitioner at a specified dosage and route of administration, but otherwise can only be supplied under the supervision of a pharmacist.

Drug interactions are always complex and in the case of HMPs, assessing the situation is even more difficult. There is a great deal of misinformation surrounding herb–drug interactions (HDIs), and animal and cell-based studies, and individual case reports where causality has not been proved, have been cited as 'evidence' for clinical HDIs. The potential for interaction is variable, but most likely when patients are on cardiovascular, immunosuppressant and CNS drugs. All practitioners wisely err on the side of caution when warfarin, statins and digoxin are involved, as well as ciclosporin and tacrolimus, and midazolam and phenytoin, and this is equally true when combined with HMPs. St. John's wort has become notorious for its interaction profile, and should be avoided with the drugs mentioned, although it is in fact a very safe drug when used alone. In the monographs for the herbal drugs in this book, important HDIs are specified and warnings given when there may be a risk, even if not proved clinically; for more information on mechanisms and individual reports, see *Stockley's Herbal Medicines Interactions* (Williamson et al. 2013b).

The data available on clinically validated cases are limited and often do not allow an evidence-based decision. It is especially important that patients suffering from renal failure or liver disorders are assessed, but data is rarely available in these cases. If in doubt, the HMP should be avoided or discontinued, because the evidence in favour of the efficacy of the prescribed medicines will almost certainly be far greater. Despite the exaggerations, there is a real issue surrounding HDIs, and there is also likely to be an under-reporting of such cases, for example, via the Yellow Card Scheme (Da Costa Rocha et al. 2012). This is further explained later.

Some common safety issues to be considered during a consultation or when using HMPs are given in Table 1 using four important and commonly used HMPs as examples.

Further risks and pharmacovigilance: Patients may not read the PIL now supplied with each registered HMP, which includes warnings and information on contraindications, possible adverse reactions or interactions with other medicines, and could consume the product inappropriately. This again highlights the responsibilities of pharmacists and other health care professionals in advising patients.

Pharmacovigilance is a critical task in ensuring the safe use of HMPs. However, since the information on an HMP is often limited, this is even more challenging than it is for conventional medicines (Jordan et al. 2010). The UK Commission on Human Medicines (CHM) has extended its Yellow Card Scheme for adverse drug reaction (ADR) reporting to all hospital and community pharmacists, as well as to any member of the public. For the Yellow Card Scheme to be effective, patients need to be aware that they can report any suspected side effect associated with their medicines, including OTC and herbal products. *Thus, pharmacists have an important role to play in ADR reporting for herbal medicines. Community pharmacists should encourage patients to submit completed forms to the Medicines and Health care Products Regulatory Agency (MHRA).* As some patients may require assistance in completing these forms, the pharmacist is ideally placed to help patients with this process and, in particular, to decide whether a possible side effect is due to a medicine, or whether the MHRA criteria for reporting are met. Patient reporting of possible adverse effects has several advantages, including making the system faster, and by providing more detailed information of aspects such as how it has affected their quality of life. This should never exclude reporting by a health care

Table 1 Safety of HMPs: four examples of botanical materials and potential risks associated with their use

Herbal medicine	Contraindications	Adverse effects	Interactions with other drugs
St. John's wort (*Hypericum perforatum* L.)	Pregnancy, lactation	Gastrointestinal symptoms, allergic reactions	Can reduce the effects of warfarin and related drugs, digoxin, opioids, hormonal contraceptives, voriconazole, protease inhibitors (indinavir), statins (simvastatin and atorvastatin but not pravastatin). Serotonin syndrome has been reported in patients taking SNRIs, SSRIs and triptans.
Black cohosh (*Actaea racemosa* L.)	Pregnancy, lactation, hormone-dependent tumours	Occasionally upset stomach	Possible interactions with antineoplastic drugs such as cisplatin (experimental-based evidence only). Contains oestrogenic compounds. Might have an additive or antagonist effect in women receiving chemotherapy (tamoxifen) or hormone antagonists.
Ginseng (Asian) (*Panax ginseng* C.A.Mey)	Hypertension	Insomnia, hypertension and oedema as symptoms of overdose	Can increase the effect of antidiabetics. Might decrease the effect of tamoxifen and other oestrogen antagonists. Might reduce the effect of warfarin and related drugs (Asian and American ginseng)
Ginkgo (*Ginkgo biloba* L.)	Hypersensitivity to ginkgo preparations	Mild gastrointestinal symptoms, headaches, rare allergic reactions	Case reports describe seizure with antiepiletics (valproate and phenytoin). Might lead to haemorrhage when in combination with antiplatelet drugs (aspirin, clopidogrel and ticlopidine) and warfarin. May increase the effect of calcium channel blockers (nifedipine). Induces the metabolism of proton pump inhibitors (omeprazole). Coma development in an elderly patient taking trazodone.

Taken from Williamson et al. 2013b and Heinrich et al. 2012

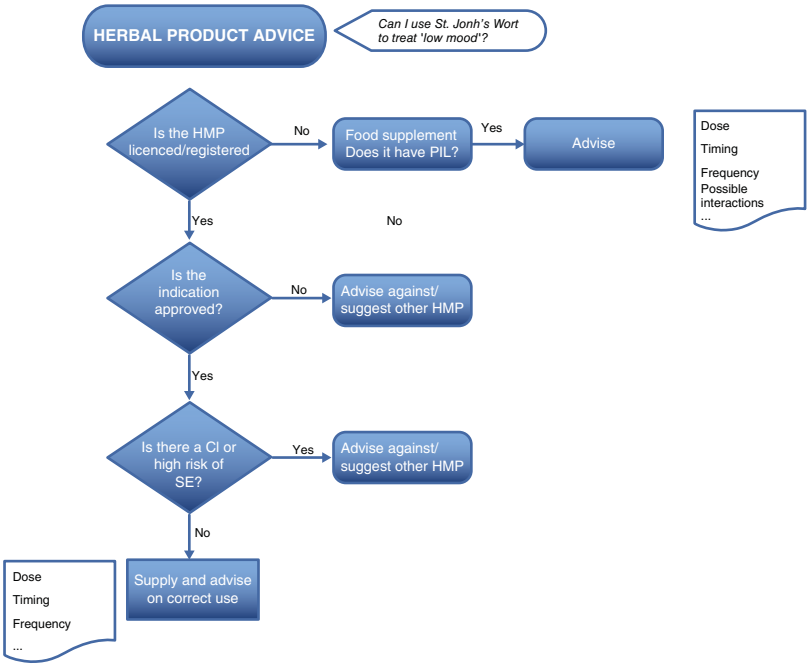

Figure 3 The key points to consider in consultations regarding HMPs. Abbreviations: HMP: herbal medicinal product; PIL: patient information leaflet; CI: contraindications; SE: side effects.

professional in parallel; pharmacists, for example, should not be concerned about the possibility of duplication of the reports and the information provided should be as detailed as possible to allow cross-checking. The MHRA is interested in any ADR reports, but specifically the ones by groups at increased risk, like children and the elderly.

Practical advice: The most important points to keep in mind during a consultation about HMPs are summarised in the flow chart above (Figure 3), which assumes that the patient is seeking help in the treatment of a self-limiting minor condition, and not one which requires medical attention.

The changes in the regulation of HMPs outlined in the introduction have brought new responsibilities for pharmacists. During a consultation with a patient, it is necessary to determine whether the herbal product is registered as herbal medicine (i.e. has a THR number on the packaging and includes a PIL), is a licensed medicine (has a product licence PL number or a marketing authorisation MA number), or is a food supplement.

Particular caution must be exercised if a patient is taking an unlicensed or unregistered product, which will not include a PIL. All health care professionals should be aware of the key points resulting from these changing responsibilities:

- HMPs and food supplements are increasingly popular for self-treatment.
- HMPs are pharmacologically active and should be treated as if they are conventional medicines; use the Yellow Card Scheme to report suspected adverse events.

- Patients should be advised to use only licensed/registered HMPs wherever possible.
- HMPs should only be used for *minor self-limiting diseases*, such as the common cold, or the temporary relief of mild anxiety.
- Patients should be advised not to use herbal medicines/food supplements alongside prescribed medicines due to risk of interactions, unless they are known to be safe to use together.
- Drugs used for cardiovascular, immunosuppressant and CNS disorders are especially liable to all types of drug interaction, including HDIs.

Within the next few years, the evidence base of many HMPs is likely to increase significantly (e.g. with the application of the 'omic'- technologies), enabling a more holistic understanding of how all the constituents in a herbal medicine work together and act on biological systems. For the time being, while evidence on efficacy or mode of action may be limited, community pharmacists can rely on licensed/registered HMPs meeting the levels of quality and safety that consumers require. Finally, an aide-memoire is provided to remind health care professionals of the steps to be taken in a consultation, as shown in Figure 4.

- Does the patient belong to any of the groups at higher risk for herb-drug interactions or idiosyncratic drug reactions?
- Do their medicines belong to a high risk therapeutic area?
- What unique risks are known about this specific herbal material and of extracts or products derived from them?
- Will the product be used for a shorter or a longer period?
- How detailed is the patient's understanding of such products, their health benefits and potential risks?

Figure 4 Some simple guiding principles for advising patients.

References

Booker A, Johnston D, Heinrich M. (2012) Value chains of herbal medicines – research needs and key challenges in the context of ethnopharmacology. *Journal of Ethnopharmacology* 140(3): 624–633.

Cuzzolin L, Francini-Pesenti F, Verlato G, Joppi M, Baldelli P, Benoni G. et al. (2011) Use of herbal products among 392 Italian pregnant women: focus on pregnancy outcome. *Pharmacoepidemiology and Drug Safety* 19(11): 1151–1158.

Da Costa Rocha I, Edwards SE, Lawrence MJ, Cable C, Heinrich M. (2012) Quality and safety of herbal products: Part 1 - New legislation and production. *Pharmaceutical Journal* 288(7708–7709): 685–686.

Davidson E, Vlachojannis J, Cameron M, Chrubasik S. (2013) Best available evidence in Cochrane reviews on herbal medicine? *Evidence-Based Complementary and Alternative Medicine* 2013: 163412.

Firenzuoli F, Gori L. (2004) Echinacea for Treating Colds in Children. *Journal of the American Medical Association* 291(11): 1323–1324.

Gagnier JJ, van Tulder M, Berman B, Bombardier C. (2006) Herbal medicines for low back pain (review). *Cochrane Database of Systematic Reviews* (2): CD004504.

Gottschling S, Gronwald B, Schmitt S, Schmitt C, Längler A, Leidig E, Meyer S, Baan A, Shamdeen MG, Berrang J, Graf N. (2013).Use of complementary and alternative medicine in healthy children and children with chronic medical conditions in Germany. *Complementery Therapies in Medicine* 21(Suppl 1): S61–S69.

Heinrich, M, Barnes J, Gibbons S and Williamson EM. (2012) *Fundamentals of Pharmacognosy and Phytotherapy*. 2nd Edition. Churchill Livingston Elsevier, Edinburgh and London.

Heinrich, M., Chan J, Wanke S, Neinhuis Ch., Simmonds MSS. (2009) Local uses of *Aristolochia* species and content of Aristolochic acid 1 and 2 – a global assessment based on bibliographic sources. *Journal of Ethnopharmacology* 125(1): 108–144.

Jordan SA, Cunningham DG, Marles RJ. (2010) Assessment of herbal medicinal products: challenges, and opportunities to increase the knowledge base for safety assessment. *Toxicology and Applied Pharmacology* 243(2): 198–216.

Kim L, Wollner D, Anderson P, Brammer D. (2004) Echinacea for Treating Colds in Children. *JAMA* 291(11): 1323–1324.

Lim A Cranswick N, South M. (2011) Adverse events associated with the use of complementary and alternative medicine in children. *Archives of Diseases in Childhood* 96(3): 297–300.

Linde K, Berner MM, Kriston L. (2008) St John's Wort for major depression. *Cochrane Database of Systematic Reviews* (4): CD000448.

Liu X, Wang Q, Song G, Zhang G, Ye Z, Williamson EM. (2013) The Classification and Application of Toxic Chinese *Materia Medica*. *Phytotherapy Research* 28(3): 334–347.

MHRA. (2013) Toxic poisoning alert for online Chinese medicines http://www.mhra.gov.uk/home/groups/comms-po/documents/news/con239404.pdf (accessed July 2013).

Moerman DE, Jonas WB. (2002) Deconstructing the placebo effect and finding the meaning response. *Annals of Internal Medicine* 136(6): 471–476.

Schulz V, Haensel R, Blumenthal M, Tyler V. (2004). *Rational Phytotherapy: A Reference Guide for Physicians and Pharmacists*. 5th Edition. Springer-Verlag, Berlin.

Singhuber J, Zhu M, Prinz S, Kopp B. (2009) Aconitum in Traditional Chinese Medicine - A valuable drug or an unpredictable risk? *Journal of Ethnopharmacology* 126(6): 18–30.

Taylor JA, Weber W, Standish L, Quinn H, Goesling J, McGann M, Calabrese C. (2003) Efficacy and Safety of *Echinacea* in Treating Upper Respiratory Tract Infections in Children: A Randomized Controlled Trial. *JAMA* 290(21): 2824–2830.

Williamson EM, Lorenc A, Booker A, Robinson N. (2013a).The rise of Traditional Chinese Medicine and its *materia medica*: a comparison of frequency and safety of materials and species used in Europe and China. *Journal of Ethnopharmacology* 149(2); 453–462.

Williamson EM, Driver S, Baxter K. (Eds.) (2013b) *Stockley's Herbal Medicines Interactions*. 2nd Edition. Pharmaceutical Press, London, UK.

Witt CM. (2013) Clinical research on traditional drugs and food items – the potential of comparative effectiveness research for interdisciplinary research. *Journal of Ethnopharmacology* 147(1): 254–8.

How to use

Some notes on how to use these monographs: The monographs in the following section are for drugs which most importantly are widely sold throughout the United Kingdom, either because they:

- are registered under the MHRA's scheme as a 'Traditional Herbal Medicinal Product' (THR);
- have a *product licence* (PL);
- are widely available as a *food supplement* with some specific claims;
- are a 'herbal health product' widely available via the Internet or in specialised shops;
- or, in a few cases, are products also sold as a *medical device*.

In general, the availability of PL or THR products are indicated (top right of the monograph), but this does not imply that *all* products on the market are regulated. Species sold as food supplements of an uncertain status are not indicated. These botanical drugs are generally also important in other European countries and in many other medical systems including the United States, Canada, Australia and New Zealand. If a botanical drug is important in traditional Chinese medicine (TCM) or Ayurveda this is stated. If major toxicological concerns have been raised, this is also indicated, but this will, of course, vary depending on the exact chemical composition of the preparation and there may be (generally registered) products on the market where the toxic metabolites have been largely removed (e.g. as in the case of butterbur, *Petasites hybridus*).

With the huge number of botanical drugs available, this has to be a selection of the most widely used species.

Excluded are all products which are not of plant or fungal origin, or which are simply sold as a food without any specific health claim.

In the top part of each monograph, key data about the drug are summarised:

- *Scientific* and (the most widely used) *common name*.
- *Synonyms*: these are Latin names under which information on these species may also have been published and are essential both for identifying which material may be in a product or for finding additional information.
- *Family*: The plant (or fungal) family that the species belongs to.
- *Other common name(s)*: Again, additional common names are included if they are frequently used in order to allow a tentative identification.
- *Drug name*: In international trade, for botanical drugs yielding licensed or registered medicines, and in many medical traditions, Latin drug names are used. They are generally found in pharmacopoeias but also in many scientific works. If a drug is included in a pharmacopeia (and, therefore, is seen as a medical substance) and has had a drug name assigned, we include it for ease of reference.

Phytopharmacy: An evidence-based guide to herbal medicinal products, First Edition.
Sarah E. Edwards, Inês da Costa Rocha, Elizabeth M. Williamson and Michael Heinrich.