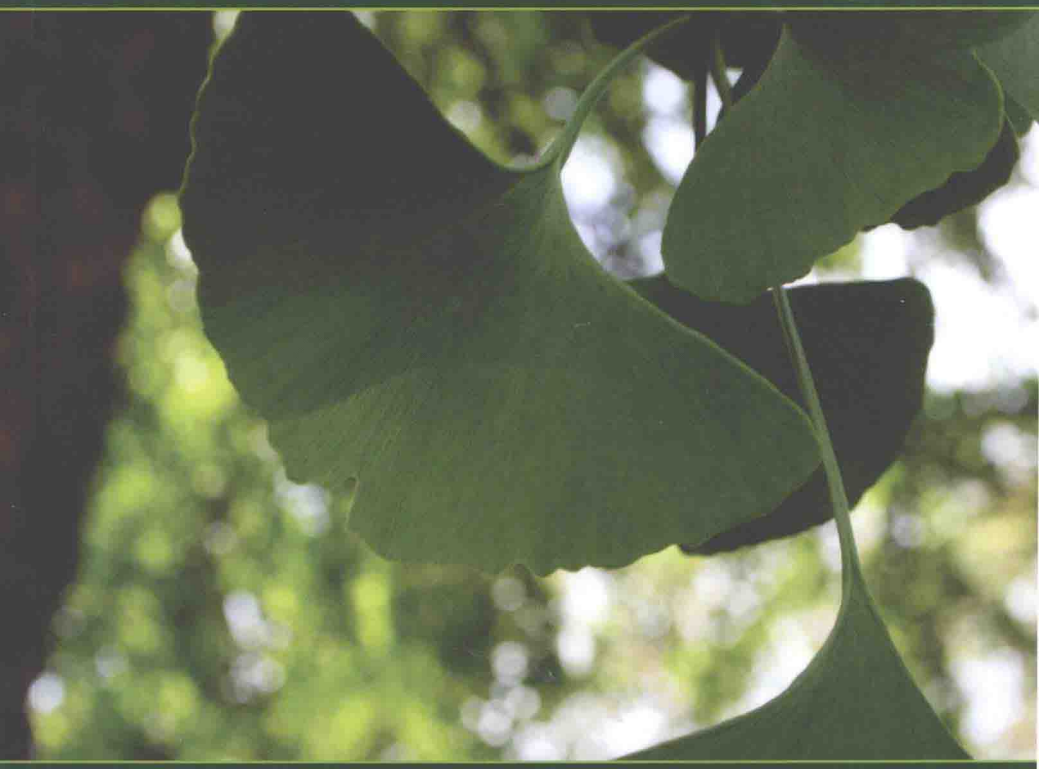
Phytopharmacy

an [redacted] Based Guide to Herbal Medicinal Products



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An evidence-based guide to herbal medicinal products

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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

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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.

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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,