# Quality, efficacy and safety of complementary medicines: fashions, facts and the future. Part II: Efficacy and safety

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This is the second of two papers which review issues concerning complementary medicines. The first reviewed the extent of use of complementary medicines, and issues related to the regulation and pharmaceutical quality of these products; the second considers evidence for the efficacy of several well-known complementary medicines, and discusses complementary-medicines pharmacovigilance. The term complementary medicines describes a range of pharmaceutical-type preparations, including herbal medicines, homoeopathic remedies, essential oils and dietary supplements, which mainly sit outside conventional medicine. The use of complementary medicines is a popular healthcare approach in the UK, and there are signs that the use of such products is continuing to increase. Patients and the public use complementary medicines for health maintenance, for the treatment or prevention of minor ailments, and also for serious, chronic illnesses. There is a growing body of evidence from randomized controlled trials and systematic reviews to support the efficacy of certain herbal extracts and dietary supplements in particular conditions. However, many other preparations remain untested. Strictly speaking, evidence of efficacy (and safety) for herbal medicines should be considered to be extract specific. Pharmacovigilance for complementary medicines is in its infancy. Data are lacking in several areas relevant to safety. Standard pharmacovigilance tools have additional limitations when applied to investigating safety concerns with complementary medicines.

*Keywords:* complementary medicines, dietary supplements, efficacy, essential oils, herbal medicines, homoeopathic remedies, pharmacovigilance, safety

## Introduction

There is a view that the criteria for efficacy and safety of complementary medicines should be the same as those for conventional drugs. Many complementary medicines, particularly herbal medicines, have a long history of traditional use. However, most are of unproven efficacy by today's standard, i.e. well-designed randomized controlled trials, and a history of traditional use does not comprise an adequate assessment of safety. The lack of evidence does not necessarily mean that complementary medicines lack efficacy or are unsafe, but that rigorous clinical investigation has not yet been undertaken and that extensive surveillance of the use of complementary medicines has not yet been carried out.

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## Efficacy

Some products, such as certain standardized herbal extracts, have undergone extensive clinical investigation, and clinical trials involving these herbal medicines have been subject to systematic review/meta-analysis, including Cochrane reviews. However, because the composition of products varies between manufacturers [1], evidence of efficacy (and safety) should be considered to be extract specific. At most, evidence should be extrapolated only to preparations of the same herb with a very similar profile of constituents. For example, most clinical trials of ginkgo (*Ginkgo biloba*) have tested the standardized ginkgo leaf extracts EGb-761 and LI-1370 [1, 2]; it should not be assumed that the results of these studies apply to other ginkgo leaf extracts, which may have a different profile of constituents, or to other preparations of ginkgo leaf, such as tinctures and teas. However, many systematic reviews and meta-analyses of clinical trials of herbal medicines ignore important details of the products tested, such as the type of extract and the formulation.

 

It is questionable though whether products containing well-tested herbal extracts have been assessed to the extent required for a UK product licence (marketing authorization). With conventional drugs, a median (range) of 1120 (43–4906) patients has been involved in clinical trials before marketing [3]. St John's wort has been tested in over 30 controlled trials involving around 3000 patients with depression, approximately half of whom will have received St John's wort. However, these studies tested different extracts of the herb and involved patients with different types of depression. Hence there may be insufficient evidence for the efficacy of one extract in a defined, licensable indication.

In contrast to certain herbal medicinal products, there is a paucity of scientific research into the effects of some types of complementary medicines, such as Bach flower remedies. It is beyond the scope of this overview to summarize all the clinical evidence relating to complementary medicines. Some of the highest level evidence and the evidence relating to some of the most popular complementary medicines is summarized below. Other research has been reviewed elsewhere [1, 2, 4–7].

In the UK, one of the reasons for the lack of research with complementary medicines is the lack of available funding. Major funding sources for medical research in the UK include the NHS and medical research charities, although these organizations spend only a small proportion of their funds on research involving complementary medicines [8, 9]. Pharmaceutical companies are another major sponsor of medical research, but some manufacturers of complementary medicines lack the resources required to carry out or fund research involving their products. Furthermore, there is little incentive to conduct research because complementary medicines, as natural products, cannot be patented, thus manufacturers do not have a protected period in which they can recoup financial returns on investments in research and development. Also, at present, many complementary medicines can be marketed without undergoing the stringent testing procedures required to obtain a marketing authorization (product licence). Another reason for the lack of research is the lack of a research infrastructure; few research units have the remit to carry out research into complementary medicines, and few complementary-medicine practitioners have the research skills necessary to develop, obtain funding, conduct and publish good-quality research [10].

### *Herbal medicinal products*

There is good evidence from systematic reviews/meta-analyses (including Cochrane reviews) of randomized controlled trials for the efficacy of certain standardized herbal extracts in particular clinical conditions, e.g. standardized St John's wort extracts in relieving symptoms of mild-to-moderate depression [11], saw palmetto extracts in treating symptoms of benign prostatic hyperplasia (BPH) [12] and standardized ginkgo leaf extracts in symptomatic relief of cognitive deficiency and dementia [13]. A summary of these and several other systematic reviews [14–17] is provided in Table 1.

In some cases, further clinical trials have been carried out since these systematic reviews were published. For example, recent studies have generally confirmed that standardized St John's wort extracts are more effective than placebo in mild-to-moderate depression, and have provided some evidence that such extracts may be as effective as certain conventional antidepressant drugs, including imipramine, fluoxetine and sertraline, in relieving the symptoms of mild-to-moderate depression [18]. Some of these studies have been criticised for using doses of comparator conventional antidepressant drugs at the lower end of the therapeutic range. A randomized, double-blind, controlled trial, funded by the US National Institutes of Mental Health and the US National Center for Complementary and Alternative Medicine, reported recently that the St John's wort extract LI-160 was no more effective than placebo in patients with major depressive disorder according to DSM-IV criteria. However, the active control sertraline also failed to demonstrate a statistically significant effect over placebo for the two primary outcome measures (mean change in the Hamilton depression scale score and the incidence of full response at week 8) [19]. Thus, the results of this study appear to be inconclusive. Furthermore, it is important to emphasize that St John's wort extracts are not recommended for use in patients with major depression.

For several other standardized herbal medicinal products, there is evidence of efficacy from at least one well-designed, randomized, placebo-controlled trial. For example, a randomized, double-blind trial involving 170 women with premenstrual syndrome (PMS) who received a casticin-standardized *Vitex agnus-castus* (chaste-berry) fruit extract (ZE-440), or placebo, for three menstrual cycles found that at the end of the study, improvements in self-assessed PMS symptoms and clinical global impression scores for severity of condition, global improvement and overall benefit/risk were significantly greater in the agnus castus group ($P < 0.001$) [20]. In another randomized, double-blind trial, 143 patients with hyperlipoproteinaemia and baseline total cholesterol concentrations of $>7.3$ mmol $l^{-1}$ received a standardized globe artichoke leaf extract (CY-450) 900 mg twice daily, or placebo, for 6 weeks [21]. At the end of the study, mean total cholesterol concentrations had decreased by 18.5% to 6.31 mmol $l^{-1}$ and by 8.6% to 7.03 mmol $l^{-1}$ in the globe artichoke and placebo groups, respectively ($P < 0.0001$). However, further rigorous randomized controlled trials are required to confirm these effects, and


 

**Table 1** Summary of selected systematic reviews of clinical trials involving herbal medicines.

| *First author (year of publication)* | *Herbal product* | *Details of systematic review* | *Summary of results/conclusion*⋆ |
|---|---|---|---|
| Linde (2003; 1998 most recent substantive amendment) [11] | Oral formulations of St John's wort (*Hypericum perforatum*) extracts† | 27 RCTs involving 2291 patients with depression | St John's wort extracts significantly more effective than placebo for short-term treatment of mild to moderately severe depressive disorders |
| Wilt (2003; 2002 most recent substantive amendment) [12] | Oral formulations of saw palmetto (*Serenoa repens, S. serrulata, Sabal serrulata*) fruit extracts† | 21 RCTs involving 3139 men with BPH and flow measures, and similar to finasteride in | Saw palmetto extracts significantly more and similar effective than placebo to finasteride in improving urinary symptom scores and measures flow |
| Ernst (1999) [13] | Oral formulations of standardized ginkgo (*Ginkgo biloba*) leaf extract⋆ | Nine RCTs involving 891 patients with Alzheimer's and/or multiinfarct dementia | Ginkgo extracts were more effective than placebo in the symptomatic treatment of dementia, but further research required due to methodological limitations of several included studies |
| Pittler (2000) [14] | Oral formulations of standardized ginkgo (Ginkgo biloba) leaf extract⋆ | Eight RCTs involving 415 patients with intermittent claudication | Ginkgo extracts, compared with placebo, significantly improved pain-free walking distance, but effect size small and clinical relevance questionable |
| Stevinson (2000) [15] | Oral formulations of garlic (*Allium sativum*) (oil/powder) | 13 RCTs involving 796 patients with various disorders including CHD, hyperlipoproteinaemia, hypercholesterolaemia, hypertension | Garlic preparations significantly reduced total serum cholesterol concentrations compared with placebo, but effect size small and some studies had methodological limitations |
| Pittler (2003; 2001 most recent substantive amendment) [16] | Oral formulations of horse chestnut (*Aesculus hippocastanum*) seed extract | 14 RCTs involving 1146 patients with CVI | Horse chestnut seed extract significantly more effective than placebo in relieving symptoms of CVI, but additional studies required |
| Wilt (2003; 1997 most recent substantive amendment) [17] | Oral formulations of *Pygeum africanum* (African prune tree) extracts† | 18 RCTs involving 1562 men with BPH | *Pygeum africanum* extracts significantly more effective than placebo in improving urological symptoms and flow measures, but additional placebo-controlled studies required |

BPH, Benign prostatic hyperplasia; CHD, coronary heart disease; CVI, chronic venous insufficiency; RCTs, randomized clinical trials (controls were placebo or active treatments). ⋆See full papers for quantitative results. †Studies of both mono- and combination herbal preparations were included.

to test the efficacy of numerous other herbal medicines for which there is little or no clinical evidence.

Although rigorous clinical investigations are lacking at present for many herbs, there is a vast literature on the phytochemistry, and *in vitro* and *in vivo* pharmacological effects of medicinal plants [1, 2, 4, 22–24]. This information affords a rationale for further investigation of such plants and provides supporting data where clinical evidence exists.

### *Homoeopathic remedies*

Homoeopathic treatment has been investigated in around 200 clinical trials, and the results of these studies have been subject to systematic review and meta-analysis.

A meta-analysis of data from all placebo-controlled trials of homoeopathy was conducted to assess whether the clinical effect of homoeopathy is equivalent to that of placebo [25]. Overall, 186 trials were identified, 89 of which were eligible for meta-analysis. The results indicated that the effects of homoeopathy are not completely due to placebo; restricting the analysis to high-quality trials only reduced, but did not eliminate, the effect found. However, there was insufficient evidence to demonstrate that homoeopathy is clearly efficacious in any single clinical condition [25].

Subsequently, a second meta-analysis considered all trials of 'individualized' homoeopathy (i.e. where patients are prescribed the remedy most appropriate for their particular symptoms and personal characteristics) [26]. This study pooled the results of 19 placebo-controlled trials and reported that individualized homoeopathy was

significantly more effective than placebo. However, when the methodologically best trials only were considered, no effect over that of placebo was seen for homoeopathy. The authors concluded 'The results of the available randomized trials suggest that individualized homoeopathy has an effect over placebo. The evidence, however, is not convincing because of methodological shortcomings and inconsistencies. Future research should focus on replication of existing promising studies. New randomized studies should be preceded by pilot studies' [26]. A systematic review of the quality of 59 trials of homoeopathic treatments has provided confirmation of the methodological limitations of these studies [27].

Further investigations [28] have explored the impact of study quality on outcome in the trials included in the original meta-analysis [25]. From this work, there was 'clear evidence' that studies with better methodological quality tended to yield less positive results, and suggested bias as the most plausible explanation for this [28]. Indeed, there are high-quality trials, published since Linde *et al.*'s original meta-analysis, reporting negative results [29, 30], and it seems likely that the original meta-analysis [25] 'at least overestimated the effects of homeopathic treatments' [28].

Several other systematic reviews and meta-analyses of controlled trials of homoeopathic remedies have been carried out. Several of these systematic reviews have included all controlled trials of homoeopathy as above, trials of homoeopathic treatments in a single therapeutic condition or area, such as postoperative ileus [31] or asthma [32], a specific homoeopathic remedy (such as arnica) in various conditions [33], or similar homoeopathic treatments in a single condition or similar conditions [34]. Linde *et al.* summarized this information in a systematic review of systematic reviews, which included 18 such publications [35]. Reports of new well-designed controlled clinical trials of homoeopathic remedies in various clinical conditions continue to be published. Such studies have reported statistically significant [36] and statistically nonsignificant [37, 38] results for homoeopathic treatment.

### *Essential oils*

There is a paucity of clinical research investigating the effects of essential oils and their use in aromatherapy.

Most controlled clinical trials of essential oils have investigated the antimicrobial effects of tea tree (*Melaleuca alternifolia*) oil preparations applied topically in conditions including acne, tinea pedis and onychomyosis, and peppermint (*Mentha piperita*) oil in irritable bowel syndrome (IBS).

A systematic review of four randomized trials comparing tea tree oil preparations with placebo and/or active controls reported that tea tree oil preparations 'may be effective as a treatment of acne and fungal infections', but that, at present, the evidence was not compelling [39]. A systematic review and meta-analysis of randomized controlled trials of orally administered peppermint oil preparations in patients with IBS drew cautious conclusions on the efficacy of such preparations in IBS because of methodological limitations of several of the included studies [40].

The few clinical trials that have investigated the use of essential oils in aromatherapy (i.e. applied in a vegetable carrier oil during massage) generally are of poor methodological quality and are also poorly reported [41]. Several have investigated the effects of aromatherapy treatment on anxiety. A systematic review of 12 randomized controlled trials of aromatherapy massage included six studies which tested its effects in aiding 'relaxation' [42]. Overall, these six studies suggested aromatherapy treatment had a mild, transient anxiolytic effect, compared with control. However, the studies were disparate (e.g. used different essential oils and administration regimens, and different controls) and all studies scored poorly on a scale assessing methodological quality.

Subsequently, a randomized, double-blind, placebo-controlled trial involving 66 women who were about to undergo an abortion found that inhalation of the odour of a combination of three essential oils was no more effective than placebo in reducing preprocedure anxiety [43].

### *Dietary supplements*

There is an increasing body of evidence from well-designed randomized controlled trials and, in some cases, systematic reviews and meta-analyses, to support the efficacy of certain dietary supplements in particular conditions. However, for many other supplements, data are conflicting or absent. It is beyond the scope of this article to review the evidence for all dietary supplements, thus only a couple of well-known supplements are discussed here. Authoritative summaries of the evidence for many popular dietary supplements, including vitamins and minerals, are given elsewhere [6, 7].

*Glucosamine* Glucosamine is a hexosamine sugar composed of glucose and the amino acid glutamic acid. It is present in the body, particularly in cartilage, where it is involved in maintaining the strength and elastic properties of cartilage. Glucosamine, usually in the form of glucosamine sulphate, has been tested in around 40 clinical trials involving patients with osteoarthritis, although many studies were limited by methodological flaws [7]. A Cochrane systematic review included 16 randomized controlled trials of glucosamine in the treatment of


 

osteoarthritis [44]. Glucosamine was reported to be superior to placebo in 12 of the 13 placebo-controlled trials. A subsequent meta-analysis broadly supported these findings, but again drew attention to methodological limitations of many studies [45].

On balance, these findings suggest that glucosamine supplementation may be an effective approach to the short-term symptomatic management of osteoarthritis, but further, longer term, well-designed, randomized, controlled trials are required to establish its benefits more definitively, and to determine whether glucosamine can alter disease progression [7]. The latter was explored in a randomized, placebo-controlled trial involving 212 patients with osteoarthritis of the knee who received glucosamine sulphate 1500 mg daily for 3 years [46]. An intention-to-treat analysis found that joint-space narrowing occurred with placebo but not glucosamine, and that the difference was statistically significant (mean, 95% confidence intervals: 0.24, 0.01–0.48; $P = 0.043$). The authors stated that it was not possible to determine whether this effect on joint-space narrowing would be clinically significant in the longer term [46].

*Melatonin* Melatonin (*N*-acetyl-5-methoxytryptamine), a hormone synthesized by the pineal gland, regulates the sleep–wake cycle. Melatonin has been tested in randomized controlled trials mainly for its effects in preventing and treating 'jet lag'. A Cochrane review of 10 randomized controlled trials of melatonin found that melatonin 0.5 or 5 mg daily taken at a time corresponding to bedtime at the journey's destination decreased jet lag in individuals who had crossed five or more time zones [47]. Time to sleep onset and sleep quality were improved with melatonin 5 mg rather than 0.5 mg. Although the findings of this review are positive, others have drawn attention to conflicting results and methodological limitations of some studies [6].

## Safety

The risks of a medical intervention for a particular patient, as well as its benefits, should be considered before use. However, benefit–risk assessments for complementary medicines are difficult as information is lacking in several areas relevant to safety. This section will focus on herbal medicines, as these are among the most widely used 'complementary medicines' in the UK and, from a biomedical perspective, are likely to have the greatest potential in terms of risk.

In the case of herbal medicines, generally, data are lacking on:

- active constituents; metabolites
- pharmacokinetics
- pharmacology
- toxicology
- adverse effects and their frequencies; effects of long-term use
- drug–herb interactions; interactions with food, alcohol
- use in specific patient groups: children, elderly, individuals with renal or hepatic disease, gender effects, individuals with a different genetic profile
- contraindications and warnings; use in pregnancy and lactation.

This lack of information also makes it difficult to compare the benefit–risk profile of certain herbal medicines with that of conventional drugs, where similar effectiveness has been shown. On the basis of clinical trial data, some herbal medicines have been shown to have a more favourable safety profile than conventional drugs of similar effectiveness. For example, in randomized controlled trials involving patients with depression, the frequency of adverse effects with extracts of St John's wort is significantly lower than that for conventional antidepressants [11]. Findings in a similar direction have been reported for extracts of saw palmetto, compared with finasteride, in randomized controlled trials in men with BPH [12]. However, it cannot be assumed that this will apply to all comparisons of herbal medicines and conventional drugs: benefit–risk comparisons must be made for each case. Nor should it be assumed that a benefit–risk analysis is applicable to all preparations of a particular herb. As with evidence of efficacy, evidence of safety should be considered to be extract specific or, at most, extended only to preparations of the same herb with a very similar profile of constituents.

Generally though, little is known regarding adverse effects of herbal medicines and their frequencies. There is a common misconception that because herbs are natural, they are entirely 'safe'. Clearly, this is not the case (many plants are inherently poisonous), and plants used medicinally do, in some cases, cause adverse effects. Such effects are not limited to type A adverse drug reactions (ADRs), i.e. those that are common, dose-related, and pharmacologically predictable, nor are they always minor in nature. ADRs associated with herbal medicines include type B reactions (those that are uncommon, unpredictable, unrelated to dose and usually serious), as well as those that occur with chronic use, and delayed effects occurring remote from drug use in the user or offspring (e.g. carcino- and terato-genic reactions) [48]. Some important safety concerns that have arisen with particular herbal medicines are discussed below. However, it is beyond the scope of this article to review information on safety aspects of all herbal and complementary medicines. Much of this information has been summarized elsewhere [2, 4, 6, 7, 48–58].

### *Kava*

Kava (also known as kava-kava; *Piper methysticum*) root is used ceremonially in most Pacific Islands as an intoxicating beverage. In developed countries, standardized extracts of kava are used to help relieve anxiety and stress. Medical herbalists also use preparations of kava in their practice.

In 2001, 30 cases of hepatotoxicity associated with the use of kava extracts were reported from Germany and Switzerland, although some of these reports appeared to be duplicates. These cases range from abnormal liver function to liver failure; one case has been fatal, and four or five others have required liver transplants. It is difficult to assess causality in these cases as, with most, the evidence is complicated by other factors, e.g. concomitant drugs which have themselves been associated with liver toxicity. Nevertheless, the majority of the herbal sector in the UK voluntarily withdrew kava products from sale, pending a decision by the Committee on Safety of Medicines (CSM) and Medicines Control Agency (MCA). By July 2002, the MCA had received 68 case reports of hepatotoxicity worldwide, including the UK [59]. The CSM's advice was that the benefit–risk profile of kava appears to be negative and on 13 January 2003 a statutory order came into effect in the UK prohibiting the sale, supply and import of unlicensed medicines containing kava [60].

### *Interactions with conventional drugs*

Where herbal medicines or dietary supplements are used concomitantly with conventional drugs, there may be a potential for drug–herb or drug–supplement interactions to occur. Also, herb–herb or supplement–supplement interactions may occur where several products are used concurrently. It should come as no surprise that these groups of pharmacologically active substances may interact with conventional drugs.

However, for the most part, knowledge of drug–herb, drug–supplement, herb–herb and other such interactions is lacking. Information is limited mainly to isolated case reports [61] and to lists of theoretical or potential drug–herb or drug–supplement interactions, predicted on the basis of what is known about the pharmacological effects of supplements and of the chemical constituents of herbal medicines [2, 7]. While these lists provide useful guidance, they are no substitute for formal studies. However, research in the area of drug–herb/supplement interactions is almost entirely lacking.

Most documented information on drug–herb interactions relates to preparations of St John's wort. In 1999, evidence emerged of pharmacokinetic interactions between St John's wort products and certain conventional drugs (warfarin, digoxin, theophylline, cyclosporin, HIV protease inhibitors, anticonvulsants and oral contraceptives) [18]. St John's wort products appear to induce certain cytochrome P450 (CYP) drug-metabolizing enzymes, including CYP3A4, CYP1A2 and CYP2C9 (thus leading to a loss of or reduction in the therapeutic activity of drugs metabolized by these enzymes), and to affect P-glycoprotein (a transport protein). There is also the potential for pharmacodynamic interactions to occur between St John's wort products and, for example, selective serotonin reuptake inhibitors (e.g. fluoxetine) and triptans (e.g. sumatriptan) [18].

### *Identifying ADRs associated with herbal medicines*

At present, the main system for generating signals of potential safety concerns associated with herbal medicines is the MCA's yellow card scheme for ADR reporting. The scheme has always applied to licensed products, including licensed herbal medicines and licensed dietary supplements (e.g. certain vitamin and mineral preparations), and was extended to include reporting on unlicensed herbal products in October 1996 by professions included in the yellow card scheme [62]. While the MCA does not formally request reports of suspected ADRs associated with other types of unlicensed products, it is unlikely that the MCA would ignore a genuine report of a serious suspected ADR associated with a nonherbal unlicensed product.

The extension of the yellow card scheme to unlicensed herbal products followed the findings of a study of traditional remedies and food supplements carried out by a UK Medical Toxicology Unit. Over a 5-year period, almost 1300 enquiries were received from healthcare professionals regarding suspected ADRs associated with these types of products [63]. In 12 cases, the relationship between the product and the ADR was confirmed, in 35 cases it was deemed 'probable' and in 735 cases 'possible'. Several reports of suspected ADRs associated with homoeopathic remedies were also received, although homoeopathic products were not included in the study [63].

In November 1999, the yellow card scheme was further extended to include reporting by all community pharmacists (hospital pharmacists were granted reporter status in April 1997); community pharmacists were asked by the MCA to concentrate on areas of limited reporting by doctors, namely conventional OTC medicines and herbal products [64].

There is no mandatory manufacturer reporting of suspected ADRs associated with complementary medicines, except for licensed products. However, the British Herbal Medicine Association (BHMA), whose members include many manufacturers of herbal products, has a


 

voluntary code of practice for members which requires that manufacturers send reports of suspected ADRs associated with unlicensed herbal products to the BHMA which may, at its discretion, forward such reports to the MCA.

In the year 2000, the MCA received almost 140 reports of suspected ADRs associated with herbal products. For the period 1996 (when the yellow card scheme was extended to unlicensed herbal products) to 2000, around 320 such reports were received. Of these 320, over a quarter describe suspected ADRs associated with St John's wort, and many of these relate to reports of interactions between St John's wort and conventional drugs (see Interactions with conventional drugs).

### *Pharmacovigilance of complementary medicines*

Pharmacovigilance for complementary medicines is in its infancy. Generally, there is a lack of clinical trial data for complementary medicines and, in any case, controlled clinical trials have the power only to detect common, acute adverse effects. Post-marketing surveillance studies with certain herbal medicines have been conducted by some manufacturers (usually those based in Germany), but this is the exception. Other tools used in pharmacovigilance of conventional drugs, such as prescription event monitoring (PEM) methodology ('green cards') and the General Practice Research Database (GPRD), now managed by MCA, are of little use, as general practitioners (who provide the data collected by both these tools) may be unaware of their patients' use of complementary medicines and, even if they are, are unlikely to record this.

In addition, there are several factors which make pharmacovigilance for complementary medicines more difficult than for conventional medicines. The yellow card scheme for ADR reporting, the principal tool used in complementary-medicines pharmacovigilance at present, has recognized limitations, including the poor quality of some reports, and the difficulty in establishing causality. An important limitation is underreporting and, for several reasons, this is likely to be greater for complementary medicines than for conventional drugs. Because of the belief that complementary medicines are natural and safe, consumers may not associate ADRs with their use [52]. Furthermore, users of herbal medicines may be reluctant to report ADRs associated with these products to their GP or pharmacist [65], and some healthcare professionals may be unaware that the yellow card scheme accepts reports for herbal products [66].

Another issue relates to the reporting of ADRs which may first be identified outside the formal system. Complementary-medicine practitioners, including medical herbalists, are not formally included in the MCA's yellow-card scheme. The National Institute of Medical Herbalists (NIMH), the major organization for herbal practitioners in the UK, does have its own 'yellow card' scheme, based on the MCA scheme, which sends a summary report annually to the MCA. For the period January 1994 to November 2001, 23 'yellow card' reports were received by the NIMH [67]. Underreporting may be a problem with this scheme, as with other spontaneous reporting schemes. Also, health-food stores are a major outlet for complementary medicines, but it is not known if staff in such outlets receive reports of suspected ADRs associated with such products, or what action they take if they do.

Tools for investigating the safety of complementary medicines need to be developed. To this end, a feasibility study is planned to determine whether modified PEM methodology (involving provision of data by medical herbalists in addition to GPs) can be applied to herbal products as prescribed by medical herbalists [68]. In the longer term, consideration could be given to the development of a Pharmacy Practice Research Database—similar to GPRD—where community pharmacists monitor patients registered with their practice and enter relevant data on use of prescription and OTC medicines, including complementary medicines [66].

## The future for complementary medicines

On the basis of current trends in market research data, it has been predicted that sales of complementary medicines will continue to increase [69]. Longitudinal data on the utilization of complementary therapists who use complementary medicines in their practice, such as medical herbalists, homoeopaths and aromatherapists, are not available for the UK, although increasing numbers of such practitioners may suggest increasing public demand for treatment with these therapies.

With the traditional herbal medicinal products directive, the future is set to bring improved quality standards for herbal medicinal products from around 2004/2005—manufacturers will need to meet standards for Good Manufacturing Practice (GMP) or remove their products from the market. Initiatives involving ethnic medicines are also aimed at improving quality standards for these preparations, although as this sector is less developed in the UK, it is likely that improvements in the quality of ethnic medicines will be seen over a longer time period.

In addition to requiring compliance with quality standards, the proposed traditional herbal medicinal products directive will require manufacturers of products to be registered under the scheme, to provide evidence of the safety of their products, and to comply with standard regulatory provisions on pharmacovigilance. At the same time, the increasing use of herbal medicines, particularly

by patients using conventional drugs and those with serious chronic illness, may result in the emergence of new safety concerns, such as signals of uncommon ADRs, those occurring with long-term use, and interactions with conventional medicines.

At present, most research involving herbal medicinal products concentrates on establishing efficacy. The proposed traditional herbal medicines directive may have the effect of shifting the emphasis of herbal-medicines research from efficacy to safety. However, manufacturers who aim at obtaining full marketing authorizations (i.e. with licensed indications) via the conventional route will still have an incentive to carry out well-designed randomized controlled trials of their products.

Against a background of widespread and increasing use of complementary medicines, it is recognized that complementary-medicine practitioners need to be regulated, and that conventional healthcare professionals need to be knowledgeable about complementary medicines and therapies. The House of Lords' Select Committee on Science and Technology's report on complementary/alternative medicine (CAM) recommended statutory regulation of certain types of complementary-medicine practitioner, including herbalists, and recommended that regulatory bodies of healthcare professionals develop guidelines on competence and training in CAM (including complementary medicines) [70]. The government accepted the recommendations made in the House of Lords' report. Thus, in the future, conventional healthcare professionals should have a basic knowledge of complementary medicines and therapies, and doctors, pharmacists, and so on, may have interactions with state-registered herbal practitioners.

In its response to the House of Lords' report, the government stated that if a therapy gains a critical mass of evidence, the NHS and the medical profession should ensure that the public has access to that therapy [71]. Thus, in addition to homoeopathic treatment, which is already available through the NHS, licensed herbal medicines and licensed dietary supplements with a sound evidence base may become more widely utilised within the NHS.

A recommendation that was welcomed related to funding for research in CAM. As well as recommending that manufacturers of complementary medicines should invest more heavily in research and development, the House of Lords' report also recommended that the NHS research and development directorate and the Medical Research Council should pump-prime CAM research with dedicated funding [71]. In 2002, the UK Department of Health Research and Development programme invited applications for post-doctoral research awards in CAM [72].

Overall, it is likely that the immediate future will bring most change for herbal medicines. The effect of regulation of herbal medicinal products and herbal-medicine practitioners, training in herbal medicine for conventional healthcare professionals, and the promise of NHS provision of herbal medicines where there is sound evidence of efficacy, may be to move herbal medicines more towards the mainstream.

The future for homoeopathic remedies may be less certain. Evidence for the efficacy of homoeopathy is lacking, and several recent, well-designed randomized controlled trials have not found any evidence of benefit for homoeopathic treatment, compared with placebo. It is not clear what impact good evidence of lack of efficacy will have on current NHS provision of homoeopathy through GP prescribing of homoeopathic remedies and at the five NHS homoeopathic hospitals. This needs to be considered in the context of the current emphasis on evidence-based medicine, and the ever-increasing demands on NHS resources.

In the long term, the future for 'complementary medicines', particularly herbal medicines, may lie with pharmacogenetics and pharmacogenomics. These relatively new fields of research are widely held to be central to the discovery of new drugs and to the future of therapeutics, yet optimizing treatment on the basis of a patient's genotype has not been discussed in the context of complementary medicines. It is reasonable to assume that individuals with a different genetic profile will have different responses to herbal medicines as well as to conventional drugs.

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## References

1 Schulz V, Hänsel R, Tyler VE. *Rational Phytotherapy. A Physicians' Guide to Herbal Medicine*, Fourth Edition, Berlin: Springer, 2000.

2 Barnes J, Anderson LA, Phillipson JD. *Herbal Medicines. A Guide for Healthcare Professionals*, Second Edition, London: Pharmaceutical Press, 2002.

3 Rawlins MD, Jefferys DB. United Kingdom product licence applications involving new active substances, 1987–1989: their fate after appeals. *Br J Clin Pharmacol* 1993; **35**: 599–602.

4 Mills S, Bone K. *Principles and Practice of Phytotherapy*, Edinburgh: Churchill Livingstone, 2000.

5 Vickers A. *Massage and Aromatherapy. A Guide for Health Professionals*, London: Chapman & Hall, 1996.



 

6 Rapport L, Lockwood B. *Nutraceuticals*, London: Pharmaceutical Press, 2002.
7 Mason P. *Dietary Supplements*, Second Edition, London: Pharmaceutical Press, 2001.
8 Ernst E. Funding research into complementary medicine: the situation in Britain. *Complement Ther Med* 1999; **7**: 250–253.
9 Ernst E. Only 0.08% of funding for research in NHS goes to complementary medicine. *Br Med J* 1996; **313**: 882.
10 Vickers AJ. Reflections on complementary medicine research in the UK. *Complement Ther Med* 1999; **7**: 199–200.
11 Linde K, Mulrow CD. St John's wort for depression (Cochrane Review). In *The Cochrane Library*, Issue 1, Oxford: Update Software, 2003.
12 Wilt T, Ishani A, Stark G *et al*. *Serenoa repens* for benign prostatic hyperplasia (Cochrane review). In *The Cochrane Library*, Issue 1, Oxford: Update Software, 2003.
13 Ernst E, Pittler MH. *Ginkgo biloba* for dementia. A systematic review of double-blind, placebo-controlled trials. *Clin Drug Invest* 1999; **17**: 301–308.
14 Pittler MH, Ernst E. *Ginkgo biloba* extract for the treatment of intermittent claudication: a meta-analysis of randomized trials. *Am J Med* 2000; **108**: 276–281.
15 Stevinson C, Pittler MH, Ernst E. Garlic for treating hypercholesterolaemia. A meta-analysis of randomized clinical trials. *Ann Intern Med* 2000; **133**: 420–429.
16 Pittler MH, Ernst E. Horse-chestnut seed extract for chronic venous insufficiency (Cochrane Review). In *The Cochrane Library*, Issue 1. Oxford: Update Software, 2003.
17 Wilt T, Ishani A, MacDonald R, Rutks I, Stark G. *Pygeum africanum* for benign prostatic hyperplasia (Cochrane review). In *The Cochrane Library*, Issue 1, Oxford: Update Software, 2003.
18 Barnes J, Anderson LA, Phillipson JD. St John's wort (*Hypericum perforatum* L.): a review of its chemistry, pharmacology and clinical properties. *J Pharm Pharmacol* 2001; **53**: 583–600.
19 Hypericum Depression Trial Study Group. Effect of *Hypericum perforatum* (St John's Wort) in major depressive disorder. A randomized controlled trial. *JAMA* 2002; **287**: 1807–1814.
20 Schellenberg R. Treatment for the pre-menstrual syndrome with agnus castus fruit extract: prospective, randomised, placebo-controlled study. *Br Med J* 2001; **322**: 134–137.
21 Englisch W, Beckers C, Unkauf M, Ruepp M, Zinserling V. Efficacy of artichoke dry extract in patients with hyperlipoproteinaemia. *Arzneimittelforschung* 2000; **50**: 260–265.
22 Bisset NG, ed. *Herbal Drugs and Phytopharmaceuticals*, ed. (German edition), Wichtl M. Stuttgart: Medpharm, 1994.
23 Evans WC. *Trease and Evans Pharmacognosy*, Fifteenth Edition, Edinburgh: W.B. Saunders, 2002.
24 Wren RC. *Potter's New Cyclopedia of Botanical Drugs and Preparations* (Revised Williamson EM, Evans FJ). Saffron Walden: Daniel, 1988.
25 Linde K, Clausius N, Ramirez G *et al*. Are the clinical effects of homoeopathy placebo effects? A meta-analysis of placebo-controlled trials. *Lancet* 1997; **350**: 834–843.
26 Linde K, Melchart D. Randomized controlled trials of individualized homeopathy: a state-of-the-art review. *J Altern Complement Med* 1998; **4**: 371–388.
27 Jonas WB, Anderson RL, Crawford CC, Lyons JS. A systematic review of the quality of homeopathic clinical trials. *BMC Complement Altern Med* 2001; **1**: 12.
28 Linde K, Scholz M, Ramirez G, Clausius N, Melchart D, Jonas WB. Impact of study quality on outcome in placebo-controlled trials of homeopathy. *J Clin Epidemiol* 1999; **52**: 631–636.
29 Walach H, Haeusler W, Lowes T *et al*. Classical homeopathic treatment of chronic headaches. *Cephalalgia* 1997; **17**: 119–126.
30 Whitmarsh TE, Coleston-Shields DM, Steiner TJ. Double-blind randomized placebo-controlled trial of homoeopathic prophylaxis of migraine. *Cephalalgia* 1997; **17**: 600–604.
31 Barnes J, Resch KL, Ernst E. Homeopathy for post-operative ileus: a meta-analysis. *J Clin Gastroenterol* 1997; **25**: 628–633.
32 Linde K, Jobst K. Homoeopathy for asthma (Cochrane review). In *The Cochrane Library*, Issue 1, Oxford: Update Software, 2002.
33 Ernst E, Pittler MH. Efficacy of homoeopathic Arnica. A systematic review of placebo-controlled trials. *Arch Surg* 1998; **133**: 1187–1190.
34 Wiesenauer M, Lüdtke R. A meta-analysis of the homeopathic treatment of pollinosis with *Galphimia glauca*. *Forsch Komplementärmed* 1996; **3**: 230–236.
35 Linde K, Hondras M, Vickers A, ter Riet G, Melchart D. Systematic reviews of complementary therapies—an annotated bibliography. Part 3: homeopathy. *BMC Complement Altern Med* 2001; **1**: 4.
36 Taylor MA, Reilly D, Llewellyn-Jones RH, McSharry C, Aitchison TC. Randomised controlled trial of homoeopathy versus placebo in perennial allergic rhinitis with overview of four trial series. *Br Med J* 2000; **321**: 471–476.
37 Lewith GT, Watkins AD, Hyland ME *et al*. Use of ultramolecular potencies of allergen to treat asthmatic people allergic to house dust mite: double blind randomised controlled clinical trial. *Br Med J* 2002; **324**: 520–523.
38 Fisher P, Scott DL. A randomized controlled trial of homeopathy in rheumatoid arthritis. *Rheumatology (Oxford)* 2001; **40**: 1052–1055.
39 Ernst E, Huntley A. Tea tree oil: a systematic review of randomized clinical trials. *Forsch Komplementärmed* 2000; **7**: 17–20.
40 Pittler MH, Ernst E. Peppermint oil for irritable bowel syndrome: a critical review and meta-analysis. *Am J Gastroenterol* 1998; **93**: 1131–1135.
41 Barnes J. Aromatherapy. *Pharm J* 1998; **260**: 862–867.
42 Cooke B, Ernst E. Aromatherapy: a systematic review. *Br J General Pract* 2000; **50**: 493–496.
43 Wiebe E. A randomized trial of aromatherapy to reduce anxiety before abortion. *Eff Clin Pract* 2000; **3**: 166–169.
44 Towheed TE, Anastassiades TP, Shea B, Houpt J, Welch V, Hochberg MC. Glucosamine therapy for treating osteoarthritis (Cochrane Review). In *The Cochrane Library*, Issue 1, Oxford: Update Software, 2002.
45 Kayne SB, Wadeson K, MacAdam A. Glucosamine—an effective treatment for osteoarthritis? A meta-analysis. *Pharm J* 2000; **265**: 759–763.
46 Reginster JY, Deroisy R, Rovati LC *et al*. Long-term effects of glucosamine sulphate on osteoarthritis progression: a randomised, placebo-controlled clinical trial. *Lancet* 2001; **357**: 251–256.
47 Herxheimer A, Petrie KJ. Melatonin for the prevention and treatment of jet lag (Cochrane Review). In *The Cochrane Library*, Issue 1, Oxford: Update Software, 2002.

48 De Smet PAGM. Health risks of herbal remedies. *Drug Safety* 1995; **13**: 81–93.

49 Jonas WB. Safety in homoeopathy. In *Homoeopathy. A Critical Appraisal*, eds Ernst E, Hahn EG, Oxford: Butterworth-Heinemann, 1999: 130–136.

50 De Smet PAGM, Keller K, Hänsel R, Chandler RF, eds. *Adverse Effects of Herbal Drugs*, Vol. 1. Berlin: Springer-Verlag, 1992.

51 De Smet PAGM, Keller K, Hänsel R, Chandler RF, eds. *Adverse Effects of Herbal Drugs*, Vol. 2. Berlin: Springer-Verlag, 1993.

52 De Smet PAGM, Keller K, Hänsel R, Chandler RF, eds. *Adverse Effects of Herbal Drugs*, Vol. 3. Berlin: Springer-Verlag, 1997.

53 Ernst E, Barnes J. Treatments used in complementary medicine. In *Side Effects of Drugs*, Annual 22, ed. Aronson JK, Amsterdam: Elsevier, 1999: 511–519.

54 Cupp MJ. *Toxicology and Clinical Pharmacology of Herbal Products*. Totawa, NJ: Humana Press, 2000.

55 Williamson EM, ed. *Major Herbs of Ayurveda*. Edinburgh: Churchill Livingstone, 2002.

56 European Scientific Cooperative on Phytotherapy. *Monographs on the Medicinal Uses of Plant Drugs*, Fascicles 1 and 2 (1996), Fascicles 3, 4 and 5 (1997), Fascicle 6 (1999), Exeter: European Scientific Cooperative on Phytotherapy.

57 Upton R, ed. *American Herbal Pharmacopoeia and Therapeutic Compendium. Analytical*, Quality Control and Therapeutic Monographs. Santa Cruz, CA: American Herbal Pharmacopoeia, 1997–2002.

58 Tisserand R, Balacs T. *Essential Oil Safety. A Guide for Health Care Professionals*. Edinburgh: Churchill Livingstone, 1995.

59 Medicines Control Agency. Voluntary suspension of kava-kava sales by herbal sector following safety concerns. Http://www.mca.gov.uk [accessed 28 February 2002].

60 The Medicines for Human Use (Kava-Kava) (Prohibition) Order 2002 (SI 2002/3170). London: The Stationery Office.

61 Stockley I. *Drug Interactions*, Sixth edition, London: Pharmaceutical Press, 2002.

62 Anonymous. Extension of the Yellow Card scheme to unlicensed herbal remedies. *Curr Prob Pharmacovigilance* 1996; **22**: 10.

63 Shaw D, Leon C, Kolev S, Murray V. Traditional remedies and food supplements. A 5-year toxicological study (1991–1995). *Drug Safety* 1997; **17**: 342–356.

64 Anonymous. Extension of the Yellow Card scheme to pharmacists. *Curr Prob Pharmacovigilance* 1997; **23**: 3.

65 Barnes J, Mills SY, Abbot NC, Willoughby M, Ernst E. Different standards for reporting ADRs to herbal remedies and conventional OTC medicines: face-to-face interviews with 515 users of herbal remedies. *Br J Clin Pharmacol* 1998; **45**: 496–500.

66 Barnes J. An examination of the role of the pharmacist in the safe, effective and appropriate use of complementary medicines. PhD Thesis, University of London, 2001.

67 Broughton A. Yellow card reporting scheme. *Eur J Herb Med* 2001; **Dec**: 3–6.

68 Personal communication. Southampton: Drug Safety Research Unit, February 25, 2002.

69 Mintel International Limited. *Complementary Medicines. Market Intelligence*. London: Mintel International Ltd, 2001.

70 House of Lords Select Committee on Science and Technology. *Complementary and Alternative Medicine*, Session 1999–2000 6th report. London: The Stationery Office, 2000.

71 Department of Health. *Government Response to the House of Lords Select Committee on Science and Technology's Report on Complementary and Alternative Medicine*. London: The Stationery Office, 2001.

72 Department of Health. *Department of Health Research and Development Programme. Guidance notes for Department of Health Complementary and Alternative Medicine Post-Doctoral Awards 2002*. http://www.doh.gov.uk/research/rdi/camresearch.htm [accessed 4 November 2002].




 