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# The 'Natural Health Service': natural does not mean safe

ARTICLE

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**SUMMARY**

Plants have been used for medicinal purposes for centuries, treating everything from non-specific ailments such as backache and colds to serious conditions, including depression and cancer. In this review, a few commonly known plants with psychotropic effects (St John's wort, *Ginkgo biloba*, kava, ginseng and valerian) are discussed by way of illustration. The readers' attention is brought to important interactions between herbal remedies and conventional drugs. A background to the constituents of herbs, possible mechanisms of action and an explanation of their antioxidant properties is given.

**DECLARATION OF INTEREST**

None.

Herbal products (including vitamins, minerals and tissue extracts) are popular dietary supplements used by millions of people (DeAngelis 2003). About 80% of the world's population does not have access to Western medicine and relies mainly on traditional practices (Atherton 1994). Thousands of herbs are available worldwide and they vary from being relatively safe to potentially lethal (Corns 2003). Regulations are not strictly enforced, making it difficult to determine an accurate frequency of adverse events. Preparations often vary in strength of active constituents, dosages differ between batches, sometimes within the same brand, and products may not even contain the advertised ingredient (Cui 1994). People tend to think that herbs are safe because they are 'natural'. Doctors are not blameless in this and are prone to dismiss herbal remedies as harmless placebos. Because herbal preparations are not 'prescribed', patients unintentionally fail to inform doctors during a consultation that they are using them. Medicinal herbs are widely available from chemists, supermarkets and the internet, sometimes with unsubstantiated claims about beneficial effects (Morris 2003).

Sales of herbal remedies in Western countries have soared over the past few decades. In the USA between 1990 and 1997, there was an observed 380% increase in the use of herbal remedies, accounting for millions of dollars in sales, and 12% of Americans stated that they had used herbs in the previous year compared with 2.5% 7 years earlier (Eisenberg 1998). Of particular concern is the proportion of patients (about 20%) who are taking both prescription drugs and herbal remedies, and of these, nearly 70% do not reveal use of alternative therapies to their physicians or pharmacists. Most herbal products are sold as food supplements and are regulated under food, not pharmaceutical, legislation (Barnes 2003). This is despite clear evidence that herbs do possess pharmacological activity. The potential for unmonitored interactions between prescription drugs and herbal remedies is therefore ever present. In the Slone survey, it was revealed that 14% of the US population had taken at least one herbal preparation/natural supplement in the week before interview (Kaufman 2002). In the UK in 2005, 42% of the population were taking some form of vitamin or herbal preparation, the over-the-counter market was worth about £277 million a year, and women were apparently the biggest consumers, often buying on impulse (Godson 2005). Among people evaluated for pharmacological clinical trials, 58% had used herbal medicines within the previous month (Fugh-Berman 1999). A postal survey carried out in England in 1998 found that 22% of respondents had purchased over-the-counter homoeopathic or herbal remedies in the previous year (Thomas 2001).

## Conditions for which herbs are used

Medicinal plants are often used, with modest overall therapeutic effect, for stress relief or anxiety, headaches, sleep problems and chronic benign diseases such as fatigue and arthritis (Ernst 2004). People with cancer, chronic pain and gastrointestinal problems often resort to complementary therapies, including herbal remedies (Eisenberg 1993; Vickers 1999). Some patients feel that conventional medicines have failed and that professional help is either not immediately to hand or is too time-consuming. Cultural beliefs are also important for some. Reports of adverse effects are less prominent in the media than for orthodox drugs, adding to the erroneous assumption that using herbs is safe (Winslow 1998). None the less, patients feel a sense of control over treatment and perceive that complementary therapists offer more time, consideration and empathy.

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**BOX 1** Common plant-derived medicinal drugs

- Aspirin, derived from acetylsalicylic acid found in willow bark, was discovered a century ago
- Digoxin: in 1785, William Withering published his famous book on the medical uses of the foxglove plant *Digitalis purpurea*, and the term 'digitalis' is used for preparations containing cardiac glycosides, particularly digoxin, extracted from plants of this biennial species
- The vinca alkaloids (extracts of the periwinkle plant) are used in cancer chemotherapy
- Quinine, derived from the *Cinchona* bark, is used for malaria
- Morphine is the most active opioid alkaloid in opium, which comes from the poppy plant *Papaver somniferum*. Opium has been used for medicinal purposes for thousands of years

What is often forgotten is that nearly a third of common 'medical' drugs are derived from plants (Box 1).

### *Adverse reactions*

Reports of patients experiencing adverse reactions to herbal medicines are on the rise. Such problems are usually linked to poor quality, incorrect identification of plant species or inadequate labelling, and serious side-effects and interactions. Phytochemically mediated modulation of cytochrome P450 activity may underlie many herb–drug interactions. Despite this, the sales of herbal remedies are doubling every 4 years (Pies 2000).

It should be noted that several common foods and drinks also influence parts of the cytochrome enzyme system. Grapefruit juice is a potent inhibitor of cytochrome P450 (Bailey 2004). Conversely, vegetables such as broccoli, cabbage, and Brussels sprouts are putative cytochrome P450 inducers; they are also known sources of vitamin K. Red wine, ethanol and cigarette smoke are also believed to induce the cytochrome P450 system and have the potential to interfere with the metabolism and catabolism of many drugs. Interactions between herbs and conventional medications are unpredictable because herbal products may contain more than one active constituent and the use of several preparations is common (Canter 2004). The elderly are even more at risk because they often need several prescribed drugs and may be taking additional medicinal herbs, unbeknown to the physician. The combination of certain herbal remedies, benzodiazepines and other sedative drugs may have an accumulative effect, particularly in elderly people, in the same way that alcohol does (Dunne 1989). Many herbal products contain glucose and some preparations reduce glucose levels, so doctors need to be alert for possible plasma fluctuations in patients with diabetes.

Adverse reactions to labelled herbal products may be caused by contaminants in the preparation. For example, non-steroidal anti-inflammatory agents and benzodiazepines are found in many Chinese medicines and heavy metal contaminants such as lead, arsenic and mercury are not uncommon.

(See Key points 1.)

**KEY POINTS 1** **General facts associated with the use of herbal remedies and complementary therapies in Western countries**

- Over 50% of patients with chronic diseases use complementary medicine
- The majority of users are female
- The highest users are aged 35–60 years
- The most popular therapies are herbal medicines, acupuncture, homoeopathy, osteopathy, chiropractic and faith healing
- A substantial proportion of patients taking warfarin, digoxin or the contraceptive pill also take herbal medicines, usually without informing their doctor
- Patients need to inform their general practitioners if they are taking herbal products

(Vickers 1999)

## Free radicals

To understand the background regarding the mechanisms of action of herbal medicines it is helpful to be familiar with the concepts of free radicals and antioxidants. Atoms consist of a nucleus, neutrons, protons (positively charged particles) and electrons (negatively charged particles). The number of protons determines the number of electrons orbiting the atom in one or more shells. An atom is considered 'grounded' when each electron in the outer shell has a corresponding electron spinning in the opposite direction.

The terms 'oxidation' and 'reduction' are used to denote a loss or gain of electrons respectively. An oxidising agent or 'free radical' will therefore seek to gain or absorb free electrons. A free radical refers to any atom (e.g. oxygen, nitrogen) with an unpaired electron in its outer ring, which makes that atom unstable and highly reactive. To restabilise, the unstable atom borrows an electron from another atom (electron stealing), which in turn becomes unstable. The result is a cascade effect or chain reaction. When oxygen gains an atom, the free radical superoxide is formed, which causes cellular damage. The primary site of free radical damage is the DNA in the mitochondria, resulting eventually in destruction of fatty membranes, DNA mutation and cell death. Free radicals are very unstable, and only become stabilised because they have a predilection for stealing electrons from the lipid membranes of a cell, a process known as lipid peroxidation. Air pollution, cigarette smoke, radiation and herbicides are major sources of free radicals, producing oxidative stress.

A free radical is an atom that has one or more unpaired electrons, and because it tends to acquire an electron from other atoms it is highly reactive.



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Therefore, any free radical involving oxygen is of the reactive oxygen species (ROS), although not all reactive oxygen species (e.g. $H_2O_2$) are free radicals. Highly reactive radicals include superoxide dismutase, hydrogen peroxide and the hydroxyl molecule. Because polyunsaturated fatty acids are abundant in cellular membranes and in low-density lipoproteins, ROS-induced peroxidation of these acids causes a cascade of lipid peroxidation, inducing further oxidation of membrane lipids and proteins. Oxidative damage initiated by reactive oxygen species is thought to contribute to the aging process. Theoretically, antioxidants should therefore have a protective effect on cellular metabolism by interrupting the cascade effect. To maintain homoeostasis, a balance must occur between reactive oxygen production and removal.

The body uses antioxidants to limit excess free radical formation. Antioxidants include carotenoids, vitamins C (ascorbic acid) and E (α-tocopherol), and superoxide dismutase, an enzyme present in both the mitochondria and cytoplasm of the cell. An antioxidant protects lipids from peroxidation by free radicals by preventing electron stealing through the donation of an electron, thereby neutralising the free radical. When this occurs, the antioxidant by definition itself becomes a free radical. However, antioxidants have the ability to accommodate the change in electron status without becoming reactive because they remain stable whether or not they have donated electrons. Antioxidants therefore reduce or limit cell damage by 'mopping up' reactive oxygen species before harmful molecular changes occur. Disease and injury are believed to result when free radical formation exceeds the protective capacity of the antioxidant defence system, for example during strenuous exercise.

## Active constituents and composition of herbs

Phenols are compounds containing a benzene ring with an hydroxyl group. Flavonoids are polyphenols, and more than 4000 flavonoid types have been identified. Flavonoids are water-soluble plant pigments that act as potent antioxidants, capable of scavenging hydroxy radicals, superoxide anions and lipid peroxide radicals. As stated above, it is the imbalance between oxidant and antioxidant processes (oxidative stress) that leads to cellular damage. Polyphenols such as flavonoids and tannins (oligomeric proanthocyanidins) have been shown in *in vitro* studies to inhibit the oxidation of low-density lipoproteins, thus preventing the development of atherosclerosis. This may explain why a moderate intake of red wine, the flavonoids in which inhibit the oxidation of low-density lipoprotein and thereby interrupt the first step in atherogenesis, is purported to result in a reduced risk of coronary heart disease (Miller 1996). In addition, because of their antioxidant properties, flavonoids may improve cerebral and peripheral blood flow through nitric oxide vasodilation. Flavonoids may also block the angiotensin-converting enzyme responsible for raising blood pressure.

Flavonoids (or bioflavonoids) are found in a wide variety of substances, including tea, red wine, lager, chocolate and most plant species. Quercetin is the most abundant dietary flavonoid and is found in fruit and vegetables. In addition to flavonoids, raw herbs and their extracts contain sterols, fatty acids, glycosides, saponins, tannins and terpenes (Box 2). Black cohosh (*Cimicifuga racemosa*), for example, which is used for menopausal symptoms, contains terpenes, flavonoids and tannins.

Plant products include the leaves, stems, flowers, roots and seeds. A herbal preparation may contain a single herb or combination of herbs, sometimes contaminated with animal products, insecticides, heavy metals and minerals. Other natural factors such as rainfall, the nature of the soil, humidity and temperature also alter the pharmacological effects of medicinal plants.

## Individual herbs

### *Ginkgo biloba*

The word 'ginkgo' is derived from the Chinese *ginkyo*, meaning silver apricot. This substance is derived from one of the oldest known trees, the maidenhair. Extracts from the tree have been used in Chinese medicine for thousands of years as a treatment for asthma. Nowadays, ginkgo is used primarily for memory problems. The active ingredients include flavonoid glycosides, terpene lactones and bilobalides (Kleijnen 1992).

**BOX 2** Common constituents of plants

- *Flavonoids* Water-soluble plant pigments that act as potent antioxidants
- *Sterols* Essentially steroid molecules with hydroxyl groups attached. They include cholesterol and its derivatives
- *Alkaloids* Contain amines and water and are all nitrogen heterocyclic
- *Glycosides* Molecules comprising a carbohydrate (e.g. glycone) such as glucose and a non-carbohydrate (aglycone) such as a phenol or sterol
- *Saponins* Consist of a sugar (glycone) and a non-sugar (sapogenin) molecule. They are found in numerous plants and form a soapy froth when dissolved in water
- *Tannins* Naturally occurring plant polyphenols that form complexes with proteins and other molecules; they are particularly plentiful in teas and red wine
- *Terpenes* Hydrocarbon molecules that consist of carbon and hydrogen atoms in chains of varying length; these compounds inhibit binding of platelet-activating factor, which is normally a potent mediator of inflammation
- *Carotenoids (e.g. vitamin A)* A subclass of terpenes and include alpha-carotene and beta-carotene, lutein and lycopene, found in fruit and vegetables, notably carrots and tomatoes

Ginkgo may possess monoamine oxidase ($MAO_A$ and $MAO_B$) inhibitory activity. It also increases the synthesis of prostacycline, a prostaglandin derivative which inhibits platelet aggregation and acts as a vasodilator. Ginkgo prevents phospholipid breakdown and decreases fatty acid accumulation. It is also purported to inhibit platelet-activating factor via ginkgolide-B, leading to potential bleeding (i.e. it is postulated to work as an anticoagulant). Because of its antioxidant effects, it acts as a scavenger for free hydroxyl radicals and exhibits superoxide dismutase-like activity.

It may take up to 3 months before full therapeutic effects on memory problems are apparent. The improvement in cognitive performance and behaviour in dementia may be the result of its vasodilatory action (and therefore increased cerebral blood flow), its antioxidant properties and its ability to inhibit platelet aggregation.

A study involving 309 patients with mild to severe dementia assessed changes in cognitive impairment, daily living, social behaviour and general psychopathology (Le Bars 1997). Overall, 27% of patients achieved a 4-point improvement on the Alzheimer's Disease Assessment Scale, compared with 14% on placebo; 37% of patients were considered by relatives to have improved, compared with 23% of patients taking placebo. The improvement, although modest, was clinically significant, as it was equivalent to the average decline seen in such patients over a 6-month period and was of sufficient magnitude to be recognised by the caregivers. There were no overall changes in psychopathology between the two groups.

Another study (Kanowski 1996) involved a randomised, double-blind placebo-controlled trial of *Ginkgo biloba* in 216 out-patients with mild to moderate dementia (Alzheimer type) or multi-infarct dementia. Participants were assessed for psychopathology, memory, attention and performance of daily living activities. Improvement was significantly higher in the ginkgo treatment group. Similar improvement in cognitive performance has been demonstrated in other double-blind placebo-controlled studies (Rai 1991; Hofferberth 1994).

A meta-analysis of four studies with strict inclusion criteria for dementia revealed a small but significant improvement in cognitive function using ginkgo extract for 3–6 months (Oken 1998). The authors postulated that ginkgo protects the brain from oxidative stress by reducing cell membrane peroxidation and inhibiting platelet-activating factor.

A review of 40 controlled trials (Kleijnen 1992) revealed only 8 to be of good quality. All trials but one showed positive effects of ginkgo compared with placebo on symptoms of cerebral insufficiency, and the differences between the ginkgo and the control groups were large enough to be clinically relevant. However, cerebral insufficiency covers a wide range of symptoms, including difficulties in memory and concentration, confusion, mood disturbance, tiredness, headache, tinnitus and dizziness. Such a broad spectrum of symptoms should be taken into account when assessing outcome measures in clinical trials.

Encouraging results have also been shown in the use of ginkgo for intermittent claudication. Although the overall effect was modest, a meta-analysis of eight randomised controlled trials found ginkgo superior to placebo (Pittler 2000a). Vasodilation, inhibition of platelet-activating factor and reduced blood viscosity have all been cited for the beneficial effect of ginkgo in this condition.

### Side-effects

Ginkgo does have side-effects, although the incidence of serious adverse reactions is low. Some patients experience nausea and vomiting. Others report increased salivation, decreased appetite, headache, skin rashes, diarrhoea, restlessness, sleep disturbance and allergy to the ginkgo fruit. Because of its inhibition of platelet-activating factor, patients should be warned when ginkgo is taken with warfarin or aspirin, as cases of subdural haematoma, cerebral haemorrhage and subarachnoid haemorrhage have been reported.

## *St John's wort (Hypericum perforatum)*

St John's wort has been used as a medicinal herb for over 2000 years to treat a multitude of conditions as diverse as wound healing, chronic fatigue syndrome, renal disease and even insect bites. Today, it is most commonly used as an antidepressant for mild to moderate depression (Ernst 2002). Its use for this purpose has been widespread in Europe, particularly Germany, for the past 50 years.

Extracts of the plant contain at least ten constituents (e.g. hypericum) that may contribute to its pharmacological effects. Reuptake of serotonin, noradrenaline, dopamine, gamma-aminobutyric acid (GABA) and glutamate into synaptosomes may be blocked and serotonin receptors down-regulated (Nathan 2001). Hypericin can inhibit benzodiazepine binding and monoamine oxidase.

A comprehensive overview (Linde 1996), including a quantitative analysis of the efficacy of St John's wort for depression, originally identified 37 randomised trials; 14 were excluded as they included only healthy volunteers and investigated physiological parameters. Of the remaining 23 trials (1008 patients), 15 were placebo controlled and 8 (749 patients) compared St John's wort with other antidepressants or sedative drugs. There was a



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significant effect of St John's wort over placebo and it was slightly better than standard antidepressants. A Cochrane review by the same authors (Linde 2000) reported similar findings. An analysis restricted to placebo-controlled studies using standardised doses of St John's wort and a standard outcome measure (e.g. the Hamilton Rating Scale for Depression) found that 61% of patients receiving the extract responded compared with 24% receiving placebo (Schultz 1994a).

### Side-effects

Side-effects of St John's wort are generally mild and include dry mouth, fatigue, constipation and increased frequency of micturition. Dizziness and restlessness may occur. Hypomania in bipolar disorder may be triggered and the combination of St John's wort with serotonin blockers could lead to serotonin syndrome (Pies 2000). Photosensitivity and, rarely, acute neuropathy may occur (Bove 1998). When activated by ultraviolet rays, hypericin can cause dermatitis and inflammation of mucous membranes. Photoactive hypericins that produce free radicals when exposed to light may be the underlying cause.

Interactions with prescribed medications are now well established, especially with the contraceptive pill, digoxin, verapamil and some immunosuppressants (e.g. cyclosporine). The interaction most likely occurs through the induction of cytochrome enzymes such as cytochrome P450 and/or P-glycoprotein (which transports proteins and lipids across cell membranes). Interference of St John's wort with warfarin metabolism leads to lower blood concentrations of the drug, and hence the risk of thrombosis. When used concomitantly with the contraceptive pill it can cause intermenstrual bleeding and reduced contraceptive efficacy.

## *Kava (Piper methysticum)*

Kava is the beverage produced from the rhizome (rootstock) of the plant *Piper methysticum*. For hundreds of years kava has been used throughout the islands of the South Pacific to relieve stress and for recreational and medicinal purposes. Today, it is mainly used for its anxiolytic and soporific effects.

*Piper methysticum* is a member of the pepper family and grows best in areas of heavy rainfall and high humidity. The roots and stumps contain the highest concentration of psychoactive substances called kavalactones and they are prepared by pounding, chewing or grinding followed by soaking in cold water. The active ingredients of kavalolactones are the kavapyrones (α-pyrones) and kawain. Kavapyrones (methysticin and dihydromethysticin) are centrally acting skeletal muscle relaxants and anticonvulsants.

Kava has been shown in a number of research-controlled trials to be effective for anxiety and insomnia. In 11 trials that met strict inclusion criteria, and a meta-analysis of 6 studies, a significant reduction in anxiety symptoms was found: adverse reactions to kava extract were mild and transient (Pittler 2000b). Kava possibly acts on $GABA_A$ receptors, blocks noradrenaline reuptake, inhibits sodium-dependent and calcium channels, and suppresses release of glutamate. Effects are experienced within 2 hours and may last for several hours.

### Side-effects

Side-effects include stomach complaints, restlessness, drowsiness, tremor, headache, tiredness and hyporeflexia. Kava may interact with benzodiazepines to cause lethargy and disorientation (Miller 1998). The most serious side-effect, though rare, is hepatotoxicity (30 cases in 2001), sometimes leading to hepatic failure (Barnes 2003). The breakdown product pipermethystine is thought to be the constituent that damages hepatic cells.

A rash is often seen, especially in heavy users, in the form of a yellowish discolouration of the skin and ichthyosiform scaling (similar to that seen in pellagra). The kava dermatopathy is often accompanied by ocular irritation. The condition completely resolves when kava is discontinued. Ataxia, hair loss and exacerbation of Parkinson's disease are other known adverse effects (Ruze 1990; Mathews 1998). Occasionally, heavy kava drinkers experience double vision. The relaxing and euphoric actions may be caused by activation of mesolimbic dopaminergic neurons.

## *Ginseng (Panax ginseng)*

The most commonly used varieties of this plant in herbal medicine are *Panax ginseng*, *P. quinquefolium* and *P. notoginseng*. One of the most highly regarded herbal medicines in the Orient, ginseng gained an almost magical reputation for its ability to promote health and prolong life. The genus name *Panax*, derived from Greek, means 'panacea' or 'all-healing'. Saponins and terpenes are the active ingredients.

Ginseng works as an antioxidant. It is a popular pick-me-up (tonic) often used for a quick energy 'fix' (it has been given to race horses for this reason) and for its aphrodisiac properties. It appears to be well tolerated, although despite being recommended for increasing stamina, overall it does not appear to enhance physical performance (Kiefer 2003). Ginseng possesses oestrogenic effects, hypoglycaemic activity and neurotransmitter reuptake inhibition of noradrenaline, serotonin, dopamine and glutamate (Fugh-Berman 1999). It has an effect on hepatic lipogenesis and glycogen

storage, which may account for its hypoglycaemic action (Ernst 2002). Ginseng may also inhibit $MAO_A$ and $MAO_B$ activity and thereby enhance the effects of monoamine oxidase inhibitors.

#### Side-effects

Ginseng's oestrogen (steroid) effects may cause vaginal bleeding and mastalgia. Other reported side-effects include insomnia (which commonly occurs), headache, hypoglycaemia, nervousness, reduced concentration, euphoria, diarrhoea, hypertension and palpitations. Caution is advised when taking warfarin because ginseng is thought to lead to inhibition of platelet aggregation by blocking $thromboxane_{A2}$ production. The latter is synthesised by platelets and promotes vasoconstriction and platelet aggregation respectively.

### *Valerian (Valeriana officinalis)*

The word 'valerian' is probably derived from the Latin *valere*, meaning 'to be strong'. The 1st-century Greek physician Dioscorides and his contemporaries wrote about valerian as *phu*, a word that probably has the same word-root as the exclamation 'phew'. The plant was perhaps rightly named in that context because of its distinctive overpowering sweet odour; it also tastes bitter. Some 250 different species exist.

Insomnia is a very common complaint in the general population and even more so in people with mental health problems. Valerian is widely used as a mild sedative to reduce insomnia, excitability and exhaustion; it also acts as a depressant on the central nervous system and has antispasmodic properties.

Considerable research has been aimed at establishing the chemical/pharmacological basis of activity. Unfortunately, valerian contains over 100 different constituents and therefore it is difficult to ascertain with certainty the basis of its mechanism of action (Beaubrun 2000). Some of its constituents have a direct action on the amygdaloid body; valerenic acid is thought to inhibit enzyme-induced breakdown of GABA in the brain, resulting in sedation – an effect similar to that of benzodiazepines; other neuroreceptors may be involved. Valerian may decrease subjective feelings of somatic arousal, in contrast to the beta-blockers, which have effects on physiological activation. Serum concentrations of valerenic acid correlate with the pharmacological activity of valerian. Aqueous extracts of the roots contain appreciable amounts of GABA, which could cause sedation; however, there is controversy surrounding the bioavailability of this compound (Houghton 1999). The large variation in dosage in reported studies leads to difficulty in establishing an effective standard product, which is important given that valerian is the most commonly used herb for insomnia throughout Europe and the USA (Bent 2004).

In a placebo-controlled trial involving 42 patients, valerian was not shown to be appreciably better in promoting sleep (Donath 2000). However, in a smaller pilot study of 14 poor sleepers, valerian extract proved effective in decreasing sleep stage 1 and increasing the percentage of slow-wave sleep, indicating that it might be beneficial for mild insomnia (Schultz 1994b). Results from a systematic review of randomised placebo-controlled trials suggest that valerian may improve sleep quality without causing side-effects (Bent 2006). The anxiolytic effects of valerian have yet to be clearly defined (Ernst 2007).

Valerian is generally well tolerated for 4–6 weeks. Effects often take at least 2 weeks to become apparent (Houghton 1999).

#### Side-effects

Valerian may cause headache, excitability, gastric upset, uneasiness, dizziness, ataxia, hypothermia and mydriasis. Hepatotoxicity has been reported (MacGregor 1989). Chronic use (for longer than 2–4 months) may, paradoxically, result in insomnia. Concentration may be reduced for several hours after taking valerian and caution is therefore advised when driving or operating heavy machinery.

## Conclusions

Medicinal herbs are easily available and widely used throughout the world, and their promotion and sale continue largely unregulated. Problems abound in establishing both their efficacy and their safety (Key points 2).

The paucity of high-quality well-controlled therapeutic trials makes results difficult to interpret, which inhibits doctors from recommending herbal remedies over conventional drugs. Available information suggests that only about 13% of case reports can be considered to provide reliable evidence for interactions between prescribed drugs and herbal medicines (Izzo 2004). Potential adverse effects are even higher (Bush 2007). Although most drug–herb interactions are clinically insignificant, some have potentially serious consequences (Key points 3).

Clinicians are confronted almost daily with patients who take herbal preparations and they are therefore well placed to offer advice about the risks and benefits pertaining to herbal products. It is no longer acceptable for the clinician simply to state that these products 'do not work' or to claim ignorance regarding their use. The belief that natural medicines are safer than synthetic drugs has gained popularity in Western cultures in recent years.



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**KEY POINTS 2** **Problems with establishing efficacy and safety**

- Herbs are not subject to the same patency laws as 'medical' drugs and manufacturers are therefore reluctant to embark on costly clinical trials. Funding is also a major obstacle
- There is a lack of hard data on the safety of herbal remedies
- Herbal medicines are sometimes contaminated with heavy metals, microorganisms, pesticides and prescription drugs
- Standardisation is difficult: preparations may consist of different plants or plant parts and varying amounts of the active constituents
- Variations in composition are also influenced by natural phenomena
- Commercial preparations may not contain the advertised ingredient at all and the amount of active constituents may not correlate with that stated on the label
- Associations between herbal ingredients and adverse effects can be difficult or impossible to establish

(After Ernst 2004)

Market-driven information on natural products is widespread and has further encouraged their use in daily life. Fortunately, advances in technology have led to the discovery of many new active and potentially active constituents of herbal medicines. A better understanding of the pharmacokinetics and bioavailability of plant medicines will help in designing proper, standardised dosages (Miller 1998). Over time, and subject to rigorous controlled trials, many other unconventional 'natural' products will undoubtedly prove beneficial as alternatives, or at least complements, to conventional medicines.

**KEY POINTS 3** **Interactions between herbal remedies and prescription drugs**

- Some herbs and plant products (even cranberry juice) interfere with warfarin metabolism, leading to risk of bleeding and altered bleeding time and coagulation rates
- Certain herbs have the potential to alter the metabolism of oestrogens and other steroids
- Additive effects may occur when patients use alcohol or benzodiazepines with sedative herbs such as kava or valerian
- St John's wort may interact with the contraceptive pill, digoxin, selective serotonin reuptake inhibitors, verapamil and some immunosuppressants (e.g. cyclosporine)
- Ginkgo and ginseng may interfere with antidepressants
- Herbs with diuretic properties may cause either lithium toxicity or reduced lithium levels

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**MCQ answers**

| 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|
| a f | a t | a f | a f | a f |
| b f | b f | b f | b f | b f |
| c f | c f | c f | c f | c f |
| d f | d f | d t | d t | d t |
| e t | e f | e f | e f | e f |


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**MCQs**

**1 The proportion of the world's population that does not have access to Western medicines is estimated to be:**

**a** 10%
**b** 20%
**c** 50%
**d** 30%
**e** 80%.

**2 The following drugs are not derived from plants:**

**a** paracetamol
**b** digoxin
**c** quinine
**d** morphine
**e** ibuprofen.

**3 Constituents of herbs include:**

**a** heavy metals
**b** animal products
**c** free radicals
**d** terpenes
**e** insecticides.

**4 The following have been associated with *Ginkgo biloba*:**

**a** increased blood viscosity
**b** increased fatty acid accumulation
**c** nephropathy
**d** insomnia
**e** weight gain.

**5 Kava (*Piper methysticum*) may cause:**

**a** congestive heart failure
**b** a bluish discolouration of the skin
**c** hypervigilance
**d** euphoria
**e** hyperreflexia.



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