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REVIEW ARTICLE

The peri-operative implications of herbal medicines

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Summary

An increasing number of patients are taking herbal medicines such as echinacea, garlic, ginkgo biloba, ginseng, St John's Wort, valerian, ephedra, kava, grapefruit juice and ginger. Although these herbal medications are considered 'natural' products that may have some benefits, adverse effects such as increased bleeding tendencies and drug interactions are associated with their use. Surgeons and anaesthetists may be unaware of their patients' use of these medications because it is common for patients not to disclose their use of this form of medication, and both surgeons and anaesthetists often fail to enquire about their use. Anaesthetists and surgeons must be familiar with the effects of herbal medicines and should specifically enquire about the use of herbal medicines during pre-operative assessment. Currently available data suggest that all herbal medicines should be ceased 2 weeks before surgery.

Keywords *Medicine*: herbal. *Anaesthesia. Complications. Drug interactions.*

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The use of complementary and alternative medicines such as herbal medicines is increasingly widespread in developed countries [1–7]. An Australian survey reported that 12% of 3000 subjects used herbal medicines [2]. Several surveys reported that 32–37% of Americans used herbal medicines in a given year [8]. In Germany, herbal medicine is very much part of medical and social culture, and tens of millions of prescriptions are written for herbal medicines each year [9].

A herbal medicine is defined as a plant-derived product used for medicinal and health purposes [1, 5]. Humans have been using plant products for medicinal purposes since the Neanderthal period, i.e. 60 000 years ago [10]. Herbal medicines include a wide spectrum of substances ranging from home-made teas prepared from collected herbs to medicinal products that are approved by national regulatory bodies [11].

At least 122 distinct chemical substances derived from plants are important pharmaceutical agents in developed countries. In the pharmacopoeias of developed countries, 25% of drugs are substances first isolated from plants and a further 25% are modifications of chemicals first found in plants [9] (Table 1).

Potential problems associated with herbal medicines in the peri-operative setting include the failure of patients to disclose usage to health care professionals, interaction between herbal medicines and conventional drugs, and associated effects that are less well-known by the medical community. These issues must be considered by anaesthetists and surgeons in the peri-operative period.

This article will review the efficacy and adverse effects of the more commonly used herbal medicines such as echinacea, garlic, ginseng, ginkgo biloba, St John's Wort, valerian, ephedra, kava, grapefruit juice and ginger, and will provide a commentary on the peri-operative implications of the use of these herbal medicines.

Methods

Sources for this review include Medline 1980–2001 (searched under the following Medical Subject Headings: Alternative Medicine, Herbal Medicine, Plant Extracts, Drug Interactions, Peri-operative Bleeding and combinations of these) and the Cochrane Library to 2001 Issue 1 (searching for published Cochrane reviews on individual herbal medicines by a keyword search of their

Table 1 Medicines derived from plants.

Drug	Plant	Use
Atropine	*Atropa belladonna*	Anticholinergic
Caffeine/theophylline	*Camellia sinensis*	Central nervous system stimulant; bronchodilator
Cocaine	*Erythoxylon coca*	Local anaesthetic
Colchicine	*Colchicine autumnale*	Anti-gout
Curare	*Chondrodendon tomentosum*	Neuromuscular blocker
Digoxin	*Digitalis purpurea* (foxglove)	Anti-arrhythmic
Ephedrine	*Ephedra sinica*	Vasoconstrictor; central nervous system stimulant
Etoposide	*Podophyllum peltatum* (mayapple root)	Cytotoxic agent
Levodopa	*Mucuna deeringiana*	Anti-parkinsonian
Morphine	*Papaver somniferum* (poppy)	Analgesic
Pilocarpine	*Pilocarpus jaborandi*	Parasympathomimetic
Salicylates (aspirin)	*Salix alba* (willow bark)	Analgesic; antipyretic
Scopolamine	*Datura metel* (henbane)	Anti-emetic
Taxol	*Yew tree*	Cytotoxic agent

common and Latin botanical names). The bibliographies of included studies were also scanned for additional references, i.e. 'reference dredging'. The following internet sites were also used: American Society of Anaesthesiologists Public Education (*http://www.asahq.org/PublicEducation*) and National Library of Medicine PubMed (*http://www.ncbi.nlm.nih.gov*).

Overview of common herbal medicines

Echinacea

Various parts of the echinacea plant have been used by Native Americans since the 1600s. Echinacea, derived from one or more of the three species (*echinacea angustifolia, echinacea pallida*, *echinacea purpurea*) is currently the top-selling herbal product in the USA [12]. The most commonly used echinacea is prepared from the 'above ground' parts of *echinacea purpurea* (purple coneflower). Echinacea extracts contain flavonoids, polysaccharides, alkylamides, chicoric acid glycosides and polyacetylenes [9, 12]. The polysaccharide, alkylamide and chicoric acid components are believed to provide the non-specific immunostimulatory activity of echinacea [12]. It has been suggested that echinacea enhances phagocytosis, resulting in activation of non-specific immunity. *In vitro* and animal studies have demonstrated that echinacea modulates cytokines and activates both macrophages and natural killer cells [13–16].

Echinacea is used for the prevention and treatment of viral, bacterial and fungal infections (especially upper respiratory tract infections), the treatment of chronic wounds and ulcers, the treatment of chronic arthritis and to decrease the adverse effects of chemotherapeutic agents [12].

In a meta-analysis of eight trials investigating the efficacy of echinacea in preventing upper respiratory tract infections [17], there were five randomised, placebo-controlled, blinded trials where the subjects used echinacea for 8–12 weeks. Only two of the five trials found a statistically significantly lower incidence of infection in the treatment group, whereas the other three trials showed only trends in favour of the treatment group [17]. The pooled sample size was inadequate because of the heterogeneity of the five trials. A recent randomised, placebo-controlled trial involving 109 patients with a history of more than three colds in the preceding year failed to show the value of echinacea as prophylaxis against the common cold [18].

Seven double-blind, randomised, controlled trials reported that echinacea decreased the severity and duration of upper respiratory tract infections [9, 19–21]. A recent randomised, controlled trial of 120 patients presenting with the first symptoms of upper respiratory tract infection reported that the duration and severity of symptoms were significantly decreased in the group treated with echinacea [22]. Although a small difference in the severity and symptoms of the common cold was found, the sample size was inadequate to detect any statistical significance. A quantitative meta-analysis could not be performed on these treatment trials because of heterogeneity of the trials [17]. Current evidence suggests that echinacea may decrease the severity and duration of upper respiratory tract infections but is not useful as prophylaxis.

Echinacea appears to have a favourable adverse effects profile [9, 23]. Although echinacea preparations contains pyrrozolidine alkaloids [24], hepatotoxicity is unlikely because these alkaloids are structurally different from the pyrrozolidine alkaloids known to be hepatotoxic [12, 25]. Adverse effects include unpleasant taste, gastro-intestinal upset, headache and dizziness. Echinacea is contra-indicated in patients with autoimmune disease, e.g. human immunodeficiency virus and systemic lupus erythematosus, and patients taking immunosuppressants [12]. Patients with allergies to plants of the daisy or sunflower families may develop allergic reactions [26].

Garlic

Garlic (*Allium sativum*) has been used for several thousand years to flavour food and for its medicinal properties. Garlic has been claimed to be beneficial in infection, tumours, diabetes, hypertension, hyperlipidaemia and atherosclerosis [27]. There is increasing interest in its antihypertensive and antihypercholesterolaemic activity [28]. Its medicinal properties are mediated by the sulphur-rich compounds in garlic that contain cysteine.

The antihypertensive effects of garlic are short lasting (< 2 h in animal studies) [28, 29]. In a meta-analysis of eight randomised, controlled trials involving 415 patients, three trials showed a significant decrease in systolic blood pressure and four studies found a decrease in diastolic blood pressure [30]. In a 10-month, double-blind, randomised, controlled, crossover trial involving 41 patients, a 5.5% decrease in systolic blood pressure was reported [31]. Currently, there is insufficient evidence for the routine clinical use of garlic as an antihypertensive.

Allicin, a thiosulphate formed when the garlic bulb is crushed, inhibits 3-hydroxy-3-methylglutaryl co-enzyme A reductase (HMG-CoA), an enzyme important in cholesterol biosynthesis, in *in vitro* studies. Four meta-analyses investigating the value of garlic in hypercholesterolaemia have been undertaken [32–35]. The most recent meta-analysis by Stevinson *et al.* [32] analysed 13 randomised, double-blind, placebo-controlled trials of hypercholesterolaemic patients and concluded that garlic was superior to placebo in decreasing total cholesterol levels (mean decrease = 0.41 $mmol.l^{-1}$). Therefore, garlic is at best only of limited usefulness in decreasing total cholesterol.

The adverse effects of garlic include nausea (6%), hypotension (1.3%) and allergy (1.1%). *In vitro* studies have demonstrated that the allicin present in garlic can inhibit platelet aggregation [36–39]. Several case reports suggest that garlic can cause bleeding tendencies. An 87-year-old man developed a spontaneous epidural haematoma associated with excessive garlic consumption (approximately 2000 mg of garlic per day, i.e. equivalent to about four cloves) [40]. There have also been several case reports of unexpected surgical bleeding associated with garlic consumption. A 72-year-old man on no medication other than garlic tablets experienced bleeding after a transurethral resection of the prostate and required repeat cystoscopy and blood transfusion. Platelet function studies performed on this patient 3 months after resuming consumption of garlic tablets demonstrated impaired platelet aggregation in the presence of collagen [41]. In another report, a healthy 32 year-old woman on no medication had significant bleeding after augmentation mammoplasty that required an evacuation of a haematoma. However, she was noted to have a prolonged bleeding time (12.5 min) before surgery. Further enquiries revealed heavy garlic intake and, after ceasing garlic, her bleeding time decreased to 6 min [42].

Ginseng

Ginseng is the most expensive and probably the most popular herb sold worldwide. There are three main subspecies of ginseng: *Panax ginseng, Panax quinquefolius* and *Panax pseudoginseng* [24]. *Panax ginseng* is the preparation most commonly used and its biological activity is ascribed to ginsenoside, a glycosylated steroid. Ginseng has been used traditionally in Chinese medicine as a stimulant, tonic and diuretic. Other purported benefits include immunomodulation, mood elevation, increased vitality and hypoglycaemia. The immunomodulatory effects have only been demonstrated in studies on mice [43, 44]. The mood elevation effects may be mediated by an increased glucocorticoid synthesis caused by ginseng that has been demonstrated in rat studies [45]. A double-blind, placebo-controlled study of 36 newly diagnosed Type II diabetics reported hypoglycaemic effects of ginseng mediated by ginsenoside Rb2 [46, 47]. *In vivo* rat studies reported increased numbers of insulin receptors and enhanced insulin release.

Anecdotal reports of adverse effects of ginseng include hypertension [5, 48–50], nervousness and insomnia [48, 49, 51], especially when taken in large doses. It is suggested that these are mediated by the central stimulant effects of ginseng [24, 48]. Skin rashes have also been reported. Weak oestrogenic properties may cause vaginal bleeding and mastalgia in some patients [24, 48]. The lack of uniformity on dose, duration of treatment, species of ginseng used, potential for contaminants in the preparation and concurrent medication makes it difficult to assess the significance of these anecdotal reports.

Ginkgo biloba

Ginkgo biloba (maidenhair tree), considered a living fossil [10], is now grown worldwide as an ornamental tree and as a source of herbal medicine. Ginkgo extract contains

several flavonoids, terpenoids and organic acids that are believed to protect vascular walls and nerve cells by acting as free radicals and by inhibiting platelet activating factors [27, 52]. It can decrease erythrocyte aggregation and blood viscosity.

Ginkgo 120 mg.day^{-1} is used to treat cognitive deficits such as Alzheimer's disease and multi-infarct dementia. It is approved for the treatment of dementia in Germany [53]. A large multicentre, randomised, placebo-controlled trial of 2020 patients with dementia reported that ginkgo stabilised and improved cognitive performance [54]. Two meta-analyses concluded that ginkgo improved the memory and concentration of patients with cerebral insufficiency [55, 56]. In the second meta-analysis, there were eight randomised, double-blinded trials that could be included in the final analysis of 40 trials [56]. There was a statistically significant improvement in the symptoms (difficulty in concentration and memory, dizziness, tinnitus, headaches) in the treated group using a dose of 120–160 mg.day^{-1} for a minimum of 3 months [56]. Reviewer bias was a methodological deficiency because the reviewers, who were familiar with the studies, were not blinded when assessing the methodological scoring of the studies.

Ginkgo has been shown to increase blood flow and to decrease blood viscosity, and is therefore also used in the treatment of peripheral vascular disease [9, 27]. A meta-analysis of eight randomised, placebo-controlled, double-blind trials by Pittler and Ernst concluded that ginkgo was superior to placebo in the treatment of intermittent claudication, with an increase of 34 m in the pain-free walking distance [57]. The clinical significance of this meta-analysis was uncertain because exercise programmes can increase the pain-free walking distance by up to 139 m [57].

The adverse effects of ginkgo are limited to mild gastrointestinal upset and headache [24, 57, 58]. Various ginkgolides, particularly ginkgolide B, have platelet activating factor (PAF) antagonist properties. These mediate the antiplatelet and anti-inflammatory properties of ginkgo. Several case reports of intracranial haemorrhage in patients using gingko have been published. Subarachnoid haemorrhage was reported in a 61-year-old man taking gingko tablets (40 mg tds) for 6 months [59]. A 72-year-old woman suffered a subdural haematoma associated with ginkgo ingestion [60]. There is a case report of bilateral subdural haematomas associated with chronic gingko ingestion in a 33-year-old woman [61], although the patient was taking paracetamol, ergotamine and caffeine at the same time. There is a case report of a 56-year-old man taking only gingko 120 mg.day^{-1} for 18 months who suffered a spontaneous right parietal intracerebral haematoma [62]. A recent case study reported that a healthy 34 year-old man who unexpectedly bled (haemoglobin concentration decreased from 16.5 g.dl^{-1} after surgery to 5.4 g.dl^{-1}) after a laparoscopic cholecystectomy for chronic calculous cholecystitis, and on further questioning revealed that he was taking two gingko tablets per day [63].

St John's Wort

St John's Wort (*Hypericum perforatum*) has been used since ancient times for depression and anxiety, and is currently widely prescribed in Germany and other European countries as an antidepressant [9, 10, 24, 27]. St John's Wort, which is extracted from the flowers and leaves, contains at least 10 pharmacologically active components such as naphothodianthrones, flavonoids, phloroglucinols and xanthones. *Hypericin* extracts inhibit serotonin reuptake into the synapse [64–66], weakly inhibits monoamine oxidases A and B in various biological depression models [66] and inhibits norepinephrine and dopamine reuptake [65]. Crude extracts of St John's Wort have a high affinity for gamma-aminobutyric acid (GABA) receptors [24, 27, 65].

A meta-analysis of 23 double-blind trials involving 1757 outpatients concluded that patients treated with St John's Wort had a response rate 2.67 times greater than the placebo group. The efficacy of St John's Wort was equivalent to that of tricyclic antidepressants in the treatment of mild to moderately severe depressive disorders [67]. Although two other meta-analyses [68, 69] also reported the effectiveness of St John's Wort in depression, a recent randomised, double-blind, placebo-controlled, multicentre trial involving 200 outpatients treated for major depression did not demonstrate a difference between placebo and St John's Wort [70]. This difference may be explained by serious methodological flaws in most of the trials assessed in the meta-analyses. Further well-designed studies need to be performed and currently the National Institute of Mental Health in the USA is funding a US$4 million multicentre trial comparing St John's Wort with a selective serotoninergic re-uptake inhibitor (paroxetine) and placebo [27, 65].

Two meta-analyses [67, 71] reported that St John's Wort was associated with significantly fewer adverse effects compared to synthetic antidepressants. In an open trial, 2.4% of 3250 patients suffered side-effects such as gastrointestinal upset, fatigue, dizziness, confusion, headache and, rarely, photosensitivity [72, 73]. As St John's Wort increased uterine tone in animal studies, it should be avoided in pregnancy [65].

Valerian

Valerian (derived from a pink-flowered perennial, *Valeriana officinalis*) has been used as an anxiolytic and to

aid sleeping. It is suggested that valerian inhibits the degradation and reuptake of GABA. Although valerian 400 mg improved sleep quality and decreased sleep latency in two double-blind, randomised, controlled trials [74, 75], a systematic review of nine randomised, placebo-controlled, double-blind trials failed to demonstrate the efficacy of valerian in the treatment of insomnia [76].

Adverse effects in patients using valerian in high doses or for a long period of time include tremor, headache and cardiac disturbances [27]. As valerian is used extensively in Europe with a good safety record (at higher doses and even in overdose), reports of liver dysfunction were considered to be idiosyncratic reactions [50].

Ephedra

Ephedra, also known as Ma Huang, is marketed under names such as 'Herbal Ecstasy', 'Natural Ecstasy', 'Cloud 9' and 'Ultimate Xphoria'. It is a Chinese herbal medicine popular in the Western World. Traditionally, it was used for asthma and bronchitis and is now used to increase energy levels, suppress appetite, stimulate the central nervous system and as an aphrodisiac [77]. Only one randomised, controlled trial of a liquid containing ephedra for the common cold is listed in the Cochrane database [78].

Ephedra contains alkaloids such as ephedrine, pseudoephedrine, methylephedrine and norpseudo-ephedrine, obtained from the roots and branches of a shrub native to central Asia [79]. Ephedrine is the predominant active component and is a non-catecholamine sympathomimetic agent that acts directly and indirectly at alpha- and beta-adrenergic receptors, causing increased blood pressure and heart rate, relaxation of bronchial and gastrointestinal smooth muscle, central nervous system stimulation and mydriasis.

There are numerous reports of adverse reactions to dietary supplements containing ephedra [78–81]. In Australia, restrictions have been placed on the ephedrine content of marketed products for several years. In the USA, where ephedra-containing products have not been restricted until recently, there have been at least 43 cases of serious adverse reactions related to the use of ephedra, including hypertension, palpitations, tachycardia, cerebrovascular accidents and seizures [80]. There are also case reports of myocardial infarction, myocarditis, fatal cardiac arrhythmias, acute hepatitis, mania, psychosis, nephrolithiasis, anxiety, tremors and insomnia [78–81].

Absolute contra-indications to products containing ephedra include ischaemic heart disease, hypertension, cerebrovascular disease, thyroid disease, diabetes, psychiatric disorders, prostamegaly and pregnancy or lactation. In fact, the risks to anyone taking ephedra are difficult to justify, as it has no demonstrated benefit.

Kava

Kava (*piper methysticum*), also known as tonga, kava kava and intoxicating pepper, is derived from the dried root of the pepper plant family, and is grown and used in the South Pacific Islands for social and ceremonial purposes [82, 83]. In addition, it is sold as an alternative medicine in health food shops to be used as an anxiolytic and sedative.

Kavalactones (also called kava pyrones), the active component of kava, cause dose-dependent effects on the central nervous system such as sedation, hypnosis and possibly anti-epileptic and neuroprotective properties. The sedative effect is produced by enhanced GABA-mediated inhibitory neurotransmission [77].

Long-term use of kava leads to abuse potential (addiction, tolerance and withdrawal) and kava dermopathy (reversible, scaly cutaneous eruptions) [82, 83].

Grapefruit juice

Grapefruit juice, a popular beverage, is purchased by 21% of US households. It contains compounds that may decrease atherosclerotic plaque formation and inhibit cancer cell proliferation [84].

Ginger

Ginger (*Zingiber officinale*) has been widely used in India and China as both a spice and a medicine for at least 2500 years. The hardy ginger plant is cultivated in most tropical countries [9, 85]. The tuberous rhizome part of ginger is used for the treatment of headaches, colds, digestive and appetite problems, and rheumatological conditions. In western herbal medicine practice, ginger (500–2000 mg) is used primarily in the prevention of motion sickness and postoperative nausea and vomiting (PONV). It is also used as an anti-inflammatory [86].

Gingerols, in particular 6-gingerol, are the active components of ginger. However, the precise mechanism of ginger's anti-emetic activity is unknown [87, 88]. Proposed mechanisms include direct stimulation of the gastro-intestinal tract, or serotonin antagonism in the gut or central nervous system [86, 87]. *In vitro* studies suggest that ginger produces its anti-inflammatory effect by inhibiting arachidonic acid metabolism [86, 88].

Ernst and Pittler performed a systematic review of the evidence from six double-blind, randomised, placebo-controlled studies of the efficacy of ginger in preventing nausea and vomiting [87]. Of the three studies on PONV, two studies suggested that ginger is equally effective as metoclopramide, and is superior to placebo. However, the pooled absolute risk decrease for the incidence of PONV indicated that there was no significant difference between ginger and the placebo groups. A recent double-blind, randomised, placebo-controlled trial, which was

not included in Ernst's systematic review, concluded that ginger was not effective in decreasing the incidence of PONV after day-case gynaecological laparoscopy [89].

Significant adverse effects for ginger have not been reported [86]. It is known that ginger inhibits thromboxane synthetase activity *in vitro* and may therefore impair platelet function [90, 91]. However, *in vivo* human studies have failed to demonstrate this effect [92]. Although there is no good evidence that ginger is harmful in pregnancy, it would be wise to avoid it, as it has been suggested that it may be mutagenic [9, 87].

Herb – drug interactions

Echinacea

Echinacea does not interact with traditional drugs. Although Miller suggested that it should not be taken with known hepatotoxic drugs such as anabolic steroids, amiodarone, methotrexate or ketoconazole [24], there are no reports of such interactions in the literature.

Garlic

Whether garlic causes prolongation of the prothrombin time is unclear. Garlic has been reported to increase the International Normalised Ratio (INR) when used in combination with warfarin [24, 93] and should therefore not be taken by patients on warfarin therapy [24, 27, 94]. Garlic should also be avoided in patients on aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) because it enhances antiplatelet activity. Garlic has been shown to have a hypoglycaemic effect in humans and it may therefore potentiate antidiabetic therapy [95].

Ginseng

A case study reported that ginseng decreased the INR in a patient taking warfarin. The patient's INR had previously been stable for 9 months when on warfarin alone [96]. Although the mechanism of this interaction is unknown, it has been suggested that ginseng should be avoided in patients on warfarin, heparin, aspirin and NSAIDs [24, 94]. The combination of monoamine oxidase inhibitors and ginseng should be avoided, as it may cause tremulousness and mania [97, 98].

Ginkgo biloba

As ginkgolides are potent inhibitors of platelet activating factor, the combination of ginkgo and NSAIDs should be avoided. There exists a case report of a man who had been taking aspirin for 3 years and who subsequently developed a spontaneous hyphema when he was commenced on ginkgo [99]. Intracerebral haemorrhage associated with warfarin combined with ginkgo has been reported [100], and the combination of warfarin and ginkgo should therefore be avoided [94].

St John's Wort

There are several important interactions between St John's Wort and traditional drugs. These are summarised in Table 2.

As St John's Wort increases serotonin levels, a serotonin syndrome may occur when it is taken with other serotoninergic drugs such as serotoninergic reuptake inhibitors and tricyclic antidepressants. Five case reports suggestive of serotonin syndrome involving elderly patients have been published in which serotoninergic reuptake inhibitors were combined with St John's Wort [101]. The combination of St John's Wort and monoamine oxidase inhibitors should be avoided [65].

St John's Wort is a potent inducer of the hepatic cytochrome P450 microsomal oxidase enzymes [65, 105, 106]. *In vitro* studies have demonstrated that St John's Wort decreases the efficacy of warfarin by this mechanism [106]. A decreased anticoagulant effect of warfarin associated with concomitant use of St John's Wort has been recorded [103]. Therefore, INR should be closely monitored when starting or stopping St John's Wort. The enzyme-inducing action of St John's Wort causes its interactions with digoxin, theophylline, cyclosporin,

Table 2 St John's Wort – drug interactions.

Interacting Drug	Effect
Antidepressants	Serotonin syndrome with serotonergic reuptake inhibitors and tricyclic antidepressants [101]
Warfarin	Decreased efficacy of warfarin [102, 103]
Digoxin	Decreased efficacy of digoxin [93, 102, 104]
Theophylline	Decreased efficacy of theophylline [93, 102, 105, 106]
Anticonvulsants	Decreased efficacy of anticonvulsants, e.g. carbemazepine, phenytoin, phenobarbitone [95]
Oral contraceptives	Breakthrough bleeding [93, 103]. No reports of unintended pregnancy [64, 102]
Antiretroviral Agents	Decreased efficacy of antiretroviral agents, e.g. idinavir, efavirenz, delavirdine, saquinavir [64, 95]
Cyclosporin	Decreased serum concentration leading to rejection of transplanted organs [65, 93, 106], e.g. heart [107], kidney [108], liver [108]
Sumatriptan	Additive serotoninergic effects [95]

anticonvulsant drugs and antiretroviral drugs. The interaction with the antiretroviral drugs is important, as it may decrease their suppression of the human immunodeficiency virus (HIV). A small study in healthy volunteers demonstrated a 57% decrease in plasma concentrations of idinivar when it was combined with St John's Wort [109].

As St John's Wort can cause photosensitivity [110], it would seem prudent to avoid it in patients taking other photosensitizing drugs such as tetracyclines, chlorpromazine, sulphonamides and retinoids [65, 111].

Valerian

As valerian causes sedation, it is advised that it should not be combined with benzodiazepines, barbiturates and alcohol [27, 93].

Ephedra

Ephedra has the potential to interact with the monoamine oxidase inhibitors, central nervous system stimulants, ergot alkaloids and xanthines, as described earlier [77, 79].

Kava

As kava causes sedation, it is suggested that it should not be combined with benzodiazepines, barbiturates and alcohol [24, 112]. Kava interacts with levodopa to potentiate Parkinsonian symptoms [112].

Grapefruit juice

Unlike other citrus juices, grapefruit juice interacts with some prescription medications, and this is particularly concerning as juice and medication are commonly consumed together at breakfast [84]. This interaction between prescription drugs and grapefruit juice results from the inhibition of the intestinal cytochrome P450 enzyme systems, e.g. cytochrome P450 3A4 (CYP3A4). Grapefruit juice inhibits CYP3A4 and therefore results in an increase in the serum concentrations of medications such as calcium channel blockers, cyclosporin, HMG-CoA reductase inhibitors, antihistamines and cisapride. Recurrent ingestion of grapefruit juice decreases CYP3A4 protein expression in enterocytes, resulting in increased bioavailability of these drugs. The active components of grapefruit juice include flavenoids and non-flavenoids. These inhibit CYP3A4 *in vitro*. However, *in vivo* studies have only indicated modest effects [84].

Ginger

No drug interactions involving ginger have been reported [86, 92]. However, caution should be taken in those patients taking anticoagulant and antiplatelet drugs because of the inhibitory effects of ginger on thromboxane synthetase *in vitro* [92].

Peri-operative implications

The use of herbal medicines in the peri-operative population has important implications for anaesthetists and surgeons. With the increasing use of herbal medicines, the failure of patients to disclose to medical practitioners their use of herbal medicines, the potential for drug interactions, and the side-effects of herbal medicines can result in unanticipated peri-operative anaesthetic or surgical problems, in addition to medicolegal liability.

Prevalence

A US survey of the general population reported a 380% increase in the use of herbal medicines between 1990 and 1997 [7]. There have also been studies that investigated the patients about to undergo surgery. In a study of 3842 patients seen in a pre-operative assessment clinic over an 11-week period, it was found that 22% of patients were using herbal medicines [3]. A survey of 376 cardiac surgical patients reported that 10% used herbal medicines before surgery [113]. A study conducted in five Californian hospitals involving 2560 patients about to undergo surgery found that 26.4% of these patients were taking herbal medications [114].

Another concern is that while the number of patients taking herbal medicines is significant and increasing, failure to disclose usage is common. A US survey of the general population found a disclosure rate of 38.5%. A survey of 325 patients in a Sydney teaching hospital Accident & Emergency Department revealed that only 35.5% herbal medicine users disclosed their use [2]. This low rate of disclosure appears to be similar to that in the surgical population, with only 17% of the previously mentioned cardiac patients discussing their use of alternative therapies with their surgeon or physician [113]. In the California hospitals study, 56.4% of surgical patients taking herbal medicines did not inform their anaesthetist of this use [114]. There are probably multiple reasons for this lack of disclosure, in particular the failure of the physician, surgeon or anaesthetist to make specific enquiries. However, anaesthetists and surgeons should be aware of any herbal medicines their patients may be taking, because of the potential peri-operative implications.

Intra-operative implications

Although there are no clear data regarding specific adverse anaesthetic interactions, herbal medicines can have potential peri-operative interactions and effects: cardiovascular instability, coagulopathy and sedation.

Adverse cardiovascular effects

Significant changes in heart rate and blood pressure during anaesthesia in patients taking herbal medicines

such as ginseng have been reported [3, 115–117]. Long-term use of ephedra results in depletion of endogenous catecholamine stores and may contribute to peri-operative haemodynamic instability [77]. Ephedra has the potential to interact with volatile anaesthetics such as halothane, resulting in ventricular arrhythmias [77, 117].

Coagulation disturbances

Also of concern is the use of regional anaesthetic techniques such as epidural and spinal anaesthesia and analgesia in patients taking herbal medicines with antiplatelet activity such as garlic, gingko or ginger. Theoretically, there is an increased potential for the development of an epidural haematoma with epidural or spinal anaesthesia, although there have been no reports of this complication.

The most important surgical interaction is unanticipated excessive bleeding associated with garlic, ginkgo biloba and ginger. The peri-operative use of NSAIDs is increasing. The use of NSAIDs in a patient taking herbal medicines such as garlic, gingko and ginger may cause increased peri-operative bleeding.

Prolongation of anaesthesia

Potentiation or prolongation of anaesthetic agents could occur with herbal medicines such as kava, valerian and St John's Wort [117]. Kava potentiates central nervous system depressants such as barbiturates and benzodiazepines, resulting in prolonged sedation [83]. Valerian increases barbiturate-induced sleep [77, 117], and as its sedative effects appear to be mediated through modulation of GABA neurotransmission, it should be expected that valerian would potentiate the sedative effects of benzodiazepines [77].

Adverse immunological effects

There is also a concern that the long-term use of echinacea (i.e. > 8 weeks) may result in immunosuppression, which may in turn result in an increased risk of surgical complications such as poor wound healing and infection [12, 118].

Drug interactions

Patients undergoing surgery are exposed to a far greater number of pharmacological agents than in their everyday life. There is therefore a greater potential for interactions between herbal medicines and drugs [119].

Currently, the American Society of Anaesthesiologists recommends that patients cease herbal medicines at least 2 weeks before surgery [120]. In March 1999, the American Society of Anaesthesiologists distributed a 2-min video titled 'Warning to Patients Taking Herbal Medications' to television stations nationwide to warn the American population of the potential problems of herbal medicines and surgery.

Our knowledge of the pharmacodynamic and pharmacokinetic properties of many of the herbal medications is incomplete, and there are no studies providing specific and clear information on adverse anaesthetic interactions. These issues need to be addressed in future studies. Surgeons and anaesthetists need to be educated about herbal medicines, and need to include a specific enquiry into the use of any herbal medicines during pre-operative assessment. Discontinuation of any herbal medicines for 2 weeks before surgery is a prudent strategy, at least until more information is available.

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