

Herbal medicines and anaesthesia

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Key points

The use of herbal medicines among patients is widespread.

A detailed drug history including herbal remedy use should be taken before operation.

Side-effects and herb–drug interactions can be significant or fatal and should be reported.

The lack of regulation means that herbal remedies can be of variable chemical content and contain toxins such as heavy metals.

The American Society of Anaesthesiology recommends that all herbal medication should be stopped for between 2 and 3 weeks before elective surgery.

The use of herbal remedies has been around for centuries and their use in both western and eastern societies are increasing. Patient surveys have reported that 12% of Americans, 12% of Australians, and 4.8% of patients in the UK use herbal remedies.¹ The World Health Organization (WHO) estimates that up to 80% of the world's population still depend on herbal medicines.

Although there has been concern in the medical community about the potential complications arising as a result of patient use of herbal medicines, the exact degree of concern remains unclear as very few of the huge number of remedies have been formally researched. The assumption by patients and healthcare professionals that these products are 'natural' and therefore safe is clearly dangerous. Many patients do not disclose their use and hence the anaesthetist may remain oblivious to potential side-effects and drug interactions.

As pharmacokinetic and pharmacodynamic data are lacking, the American Society of Anaesthesiologists recommends that patients discontinue the use of herbal medications 2–3 weeks before surgery.² However, patients are often unaware of this recommendation and, furthermore, may present for emergency surgery. There are no formal recommendations or guidelines governing their use for the perioperative period in the UK. Hence, all anaesthetists need to familiarize themselves with the potential perioperative complications that may occur.

The aim of this article was to discuss the more commonly used herbal medicines, their side-effects and their effects on the conduct of anaesthesia. These include echinacea, ephedra, garlic, ginger, ginkgo biloba, ginseng, herbal diuretics, kava, St John's Wort, and valerian.

The scale of the problem

A significant proportion of conventional drugs today originate from compounds derived from plants. The increase in use of herbal medicines may be attributed to the belief that they are

'safer' although it may also be seen as a lack of confidence in conventional treatment options especially in more chronic illnesses. Examples of chronic illnesses believed to be cured by herbal remedies include diabetes mellitus, malignancies, arthritis, and even AIDS.

Attributable side-effects of herbal medicines (Table 1) include cardiovascular instability, electrolyte disturbances, coagulation disorders, endocrine effects, hepatotoxicity, and renal failure.^{3–5} In the UK, the majority of herbal remedies are exempt from the licensing requirements set out in the Medicines Act 1968. This has come under close scrutiny as a recent report by the House of Commons Science and Technology Committee called for the NHS to cease funding homeopathy. Similarly, in the USA, herbal products are classified as dietary supplements by the Food and Drug Administration (FDA) and are not subjected to rigorous testing. Hence, herbal remedies available over-the-counter can be of variable quality and content. Heavy metals such as mercury, lead, thallium, cadmium, copper, iron, manganese, nickel, zinc, and arsenic have all been found in certain remedies.⁶

The lack of compulsory post-marketing surveillance means that the incidence and exact nature and scale of adverse effects in the UK are unknown. At an international level, more than 6000 suspected reactions were reported to the WHO before 1998 and 101 deaths were reported to the US FDA.⁴

Common herbal medicines

Echinacea

Echinacea is the most popular herbal remedy currently being used in the USA and UK. It is believed to improve the immune system through modulation of cytokine signalling and is used for the prevention and treatment of viral, bacterial, and fungal infections (especially upper respiratory tract infections). Current evidence suggests that echinacea may decrease the severity and duration of upper

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Table 1 Commonly used herbal medicines, their uses, effects and perioperative considerations

Herbal medicine	Uses	Pharmacological effects	Perioperative considerations	Discontinuation recommendation
Echinacea	Improve immune system	Modulates cytokines; stimulate macrophages and NK cells	Avoid known hepatotoxic drugs	No data available; discontinue 2 weeks before surgery
Ephedra	CNS stimulant; weight loss; asthma treatment	Sympathomimetic	Caution with other sympathomimetic; arrhythmias with halothane	Discontinue 24 h before surgery
Garlic	Treatment of hypertension, hyperlipidaemia, atherosclerosis	Anti-platelet effects	Risk of bleeding	Discontinue 7 days before surgery
Ginger	Anti-inflammatory; Anti-emetic	Inhibit serotonergic pathways; stimulate GI tract	Risk of bleeding	No data available. Discontinue 2 weeks before surgery.
Ginkgo biloba	Neuroprotective; Improve blood flow	Free radical scavenger; anti-platelet effects	Risk of bleeding	Discontinue 36 h before surgery
Ginseng	Mood enhancer; aphrodisiac	Sympathomimetic	Risk of bleeding; hypoglycaemic effect; caution with other sympathomimetic	Discontinue 7 days before surgery
Kava	Sedative; anxiolytic	Potentiate GABA mediated system	Reduce anaesthetic requirements	Discontinue 24 h before surgery
St John's Wort	Antidepressant	Inhibit MAOIs; induces cytochrome p450	Serotonergic crisis; sedative effect	Discontinue 5 days before surgery
Valerian	Anxiolytic; hypnotic	Potentiate GABA-ergic system	Reduce anaesthetic requirements	No data available; discontinue 2 weeks before surgery.

respiratory tract infections but is not useful as prophylaxis.⁵

Known side-effects include gastrointestinal disturbances, headache, and dizziness.

Its effect on the immune system means that patients who may require perioperative immunosuppression, such as transplant candidates, should be advised to avoid them. This is because although immunostimulatory in the short-term, echinacea is a potent immunosuppressant in the long-term.⁴

Chronic use of echinacea can result in hepatic failure, which can then enhance the hepatotoxic effects of drugs such as amiodarone, methotrexate and halothane.

Pharmacokinetic data on echinacea are lacking and there are no available recommendations regarding their use in the perioperative period.

Ephedra

Originating from China, ephedra (also known as Ma Huang) contains the alkaloids ephedrine, pseudoephedrine, methylephedrine, and nor-pseudo-ephedrine. Of these, ephedrine is the predominant compound. It has direct agonist effect on α - and β -adrenergic receptors and can also indirectly increase the release of norepinephrine from presynaptic neurones. Its sympathomimetic effects mean that it is marketed as a central nervous system (CNS) stimulant, weight loss supplement and in the treatment of asthma. Perhaps more worryingly, it has become a drug of abuse with street names such as 'Herbal Ecstasy' and 'Cloud 9'.

Side-effects are predictable and include palpitations, hypertension, tachycardia, stroke, and seizures. Chronic use has been associated with cardiomyopathy. Other adverse effects reported include myocardial infarction, fatal arrhythmias, acute hepatitis, and psychosis. Its sale has thus been restricted in both Australia and the USA.

The effects of ephedra on anaesthesia are partly predictable. In combination with other sympathomimetic drugs, it can result in life-threatening arrhythmias, hypertension, and hyperthermia.

Long-term use of ephedra may deplete endogenous catecholamine stores leading to further cardiovascular instability intra-operatively and tachyphylaxis to other sympathomimetic drugs. In such a situation, direct-acting sympathomimetic agents may be preferred. Fatal arrhythmias have also been reported in patients taking ephedra exposed to halothane anaesthesia.

Pharmacokinetic studies of ephedra suggest that the herb should be discontinued for at least 24 h before surgery.

Garlic

Perhaps, better known as a cooking ingredient, garlic (*Allium sativum*) has also been used for centuries for its medicinal properties. It claims to be beneficial in cardiovascular disease, diabetes, infection, and even tumours. These actions are believed to be because of the cysteine contained in garlic, which decreases thromboxane formation and alters arachidonic acid metabolism. It inhibits platelet aggregation in a dose-dependent fashion, although this has not been demonstrated consistently in volunteers.

Adverse effects of garlic include nausea, hypotension, and allergy. In addition, there have been several case reports of garlic causing bleeding problems.⁴

It can potentiate the anti-platelet effects of aspirin and non steroidal anti-inflammatory drugs (NSAIDs). This effect may be irreversible and hence patients should be advised to discontinue their use for at least 7 days before surgery.

Ginger

Ginger (*Zingiber officinale*) is marketed as an anti-inflammatory and an anti-emetic. In addition to direct stimulation of the gastrointestinal (GI) tract, it is postulated to inhibit peripheral and central serotonergic pathways. A systematic review of randomized controlled trials showed no significant difference in the incidence of postoperative nausea and vomiting between the ginger and placebo groups.⁷

It is a potent inhibitor of thromboxane synthetase enzyme that can prolong bleeding time. Risk assessment for bleeding is prudent especially when used in combination with NSAIDs and warfarin.

Ginkgo biloba

Ginkgo is believed to protect vascular walls and nerve cells by acting as free-radical scavengers and inhibiting platelet-activating factor. Ginkgo extracts contain several flavonoids, terpenoids, and organic acids. It is approved for use in Germany for the treatment of dementia after a large multi-centre, randomized controlled trial showed improved cognitive performance in patients suffering from dementia.⁸ It is also used in the treatment of peripheral vascular disease by decreasing blood viscosity and so improving blood flow to tissues.

The adverse effects of ginkgo include GI upset and headaches.

As it is a potent inhibitor of platelet activation, ginkgo should be avoided in combination with NSAIDs, aspirin, and warfarin. There are several reports of intracranial haemorrhage in patients using ginkgo.

Pharmacokinetic data suggest that patients should discontinue taking ginkgo for 36 h before surgery.

Ginseng

Ginseng is the most expensive herb sold worldwide and has been used in traditional Chinese medicine with supposed benefits such as immunomodulation, mood enhancement and aphrodisiac effects. Its pharmacological profile is incompletely understood because of the heterogeneous and sometimes opposing effects of its constituents. It has a mild sympathomimetic effect and may interact with the monoamine oxidase enzyme. The neuroprotective effect of ginseng is believed to be because of the inhibition of sodium channels in the CNS. It has hypoglycaemic activity and interferes with platelet aggregation.

Adverse effects include irritability, insomnia, and GI disturbances. It has a weak oestrogenic effect and may predispose to gynaecomastia and vaginal bleeding.

Tremor and mania have been reported with the combination of ginseng and monoamine oxidase inhibitors (MAOIs). Consequently, this combination should be avoided.

In the perioperative period, ginseng may thus increase the risk of bleeding and should be used with caution in combination with NSAIDs and warfarin. The issue of ginseng and neuroaxial block is contentious, but there are no reports of adverse outcomes in the literature.

Blood sugar monitoring intra-operatively is recommended especially in patients already on hypoglycaemic agents.

The pharmacokinetic properties of ginseng have been studied in rabbits and as it may irreversibly inhibit platelet activity, ginseng should be stopped at least 7 days before surgery.

Herbal diuretics

Herbal diuretics include dandelion, green tea, goldenseal (*Hydrastis canadensis*), saw palmetto berries, and spearmint.^{9 10} They are often marketed in combination as natural weight loss remedies and are readily available on the high streets and the internet without prescription. Their mechanism of action is uncertain but interference with the renin–angiotensin–aldosterone system is postulated. Hence, there have been reports of significant electrolyte disturbances associated with their use.⁹

Kava

Kava (*piper methysticum*) is derived from the dried root of the pepper plant family. It is used as an anxiolytic and sedative with effects mediated by potentiation of gamma-aminobutyric acid (GABA) transmission. It potentiates the effects of barbiturates and benzodiazepines. Tolerance develops after long-term use of the herb.

Side-effects include hepatotoxicity, dermatological changes and extrapyramidal-like dystonic reactions.

It increases barbiturate-induced sleep time in laboratory animals and may have local anaesthetic properties. Hence, the requirements for anaesthetic agents may be reduced. The possibility for potentiation of the sedative effects of anaesthetic agents means that kava should be stopped at least 24 h before surgery.

St John's Wort

St John's Wort (*Hypericum perforatum*) is widely used in western societies as an antidepressant and for other mood disorders. Similar to more conventional antidepressants, its effects are thought to be because of the inhibition of serotonin, norepinephrine, and dopamine re-uptake by neurones. The efficacy of St John's Wort was found to be equivalent to tricyclic antidepressants in the treatment of mild to moderately severe depressive disorders.¹¹

Reported side-effects include GI upset, fatigue, dizziness, confusion, headache, and photosensitivity. Seizures have been noted in animal models, but not to date in humans.

There are numerous important interactions between conventional drugs and St John's Wort. It can lead to a serotonergic syndrome characterized by muscle rigidity, autonomic dysfunction, and altered mental state when used in combination with drugs which also increase plasma serotonin concentrations. Hence, it necessitates precautionary measures similar to those for patients taking conventional MAOIs.

It is also a potent inducer of hepatic cytochrome P450 CYP3A4 isoform. Hence, it may significantly increase the metabolism of many concomitantly administered drugs such as alfentanil, midazolam, and lidocaine. It also induces the P450 2C9 isoform that results in the reduction in effect of warfarin and NSAIDs.

The sedative properties of St John's Wort may potentiate or prolong anaesthetic agents' effect.

Pharmacokinetic data suggest that St John's Wort should be stopped for at least 5 days before surgery. This discontinuation is especially important for patients awaiting organ transplant and hence requires immunosuppressants and patients who may require oral anticoagulation.

Valerian

Valerian (*Valeriana officinalis*) has been used as an anxiolytic and a sedative. It produces dose-dependent sedation and hypnosis and is believed to be because of inhibition of GABA breakdown and re-uptake. Adverse effects reported include tremor, headache, hepatic dysfunction, and cardiac disturbances.

In animal models, valerian increases barbiturate-induced sleep times and acutely stopping the drug may result in a withdrawal syndrome. Caution should be taken with abrupt discontinuation of use in patients who may be physically dependent on valerian because of the risk of benzodiazepine-like withdrawal. Tapering the dose may be a more prudent strategy.

Conclusion

There are currently no clear data regarding specific adverse interactions between herbal remedies and drugs used in anaesthesia. The pharmacodynamic and pharmacokinetic properties of many of these remedies have yet to be ascertained. The risk of haematoma formation post-neuroaxial block in patients taking herbal medicines which impair platelet function is unknown.

The lack of disclosure by patients may be because of a combination of ignorance and fear of prejudice from the medical community. Hence, it is prudent that anaesthetists specifically ask about their use before operation. These herbal medicines may be taken in combined preparations and patients may be oblivious to their actual content.

The American Society of Anaesthesiologists recommends that patients cease herbal medications 2 weeks before surgery. This time frame probably errs on the side of caution as some of these remedies are eliminated rapidly upon discontinuation of their use.

The use of herbal remedies and their development is constantly evolving. Hence, sources of information for the anaesthetists

should be readily available for reference. These include the National Centre for Complementary and Alternative Medicine (<http://nccam.nih.gov>) in the USA and Toxbase (www.toxbase.org) in the UK. In addition, all potential side-effects encountered must be reported to the relevant bodies.

Conflict of interest

None declared.

References

1. Skinner CM, Rangasami J. Preoperative use of herbal medicines: a patient survey. *Br J Anaesth* 2002; **89**: 792–795
2. American Society of Anesthesiology. What you should know about herbal and dietary supplement use and anesthesia. Patient Information Leaflet 2003
3. Hodges PJ, Kam PCA. The peri-operative implications of herbal medicines. *Anaesthesia* 2002; **57**: 889–899
4. Ang-Lee M, Moss J, Yuan CS. Herbal medicines and perioperative care. *JAMA* 2001; **286**: 208–216
5. Batra YK, Rajeev S. Effect of common herbal medicines on patients undergoing anaesthesia. *Indian J Anaesth* 2007; **51**: 184–191
6. Byard RW. A review of the potential forensic significance of traditional herbal medicines. *J Forensic Sci* 2010; **55**: 89–92
7. Ernst E, Pittler MH. Efficacy of ginger for nausea and vomiting: a systemic review of randomised controlled trials. *Br J Anaesth* 2000; **38**: 367–371.
8. Lebars PL, Katz MM. A placebo-controlled, double-blind randomised trial of an extract of ginkgo biloba for dementia. *JAMA* 1997; **278**: 1327–1332
9. King A, Russett FS, Generali JA, Grauer DW. Evaluation and implications of natural product use in preoperative patients: a retrospective review. *BMC Complement Altern Med* 2009; **9**: 38–45
10. Cheng B, Hung CT, Chiu W. Herbal medicine and anaesthesia. *Hong Kong Med J* 2002; **8**: 123–130
11. Linde K, Ramirez G, Mulrow CD, Pauls A, Weidenhammer W, Melchart D. St John's Wort for depression – an overview and meta-analysis of randomised clinical trials. *Br Med J* 1996; **313**: 253–258

Please see multiple choice questions 12–15.