

# Herbal Medications and their Anaesthetic Implications

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## Abstract

Products made from plants that are used to maintain or improve health have a long history of use and claimed health benefits. Most patients fail to report their usage during history taking. However, many herbal supplements have potent pharmacologic activity by themselves and, along with various additives incorporated in various preparations can contribute to adverse effects and drug interactions. The use of herbal supplements by patients in the perioperative period is common and consistent with the substantial increase in the use of alternative medical therapies. We reviewed the literature to examine the constituents, safety, pharmacokinetics, and pharmacodynamics of those herbal supplements that are commonly used. Different supplements possess antiplatelet activity, adversely interact with other drugs, have gastrointestinal manifestations, produce organ toxicities, and produce additive effects when used with sedatives. With the increasing use of herbal supplements by patients, there is now a definite need to screen patients preoperatively for use of these supplements to prevent potential adverse events that may arise from herbal medications taken alone or combined with conventional therapies during the perioperative period. The American Society of Anesthesiologists (ASA) suggests that all herbal medications should be discontinued 2 to 3 weeks before an elective surgical procedure.

## INTRODUCTION

The use of herbal medications or nutraceutical agents in the form of herbal remedies has increased significantly throughout the world. Currently, evidence is lacking regarding the effectiveness of certain herbal medications, their potential interactions, and their potential side effects with over-the-counter (OTC) or prescribed medications, and the potential side effects of herbal medications when used alone or in conjunction with OTC medications.

Unlike orthodox medicines, which consist of a single isolated principle (often synthetic), herbal medicines are plants or extracts of plants used to prevent and treat diseases and ailments or to promote health and healing or for any of such purposes.

The medical community in general and the anaesthesiologist, in particular, should be cognizant of what data of information are available regarding herbal medications. The clinical anaesthesiologists might be interested in a recent survey of 752 patients conducted within the Department of Anaesthesiology, Texas Tech University in Lulbock. The survey revealed that, of those surveyed, 32% were actively using at least one herbal agent and 70% of these patients did not inform their anaesthesiologist of such use during the routine preoperative assessment.

Although many of the herbal medicines are neither recommended nor prescribed by health care providers, an increasing number of people are taking these products on a daily basis. Because these drugs carry a potential to cause bleeding problems or to contribute to unexpected responses to anaesthetic agents, the authors review here commonly used herbs from the perspective of the anaesthesiologist.

## EPIDEMIOLOGY

The use of herbs for medical purposes has increased dramatically over the past decade. One out of every three Americans uses herbal products, but fewer than half of those individuals discuss the matter with a conventional health care provider. Consumers hold strong views about the efficacy of the supplements they take.

In the 1980s, 80% of medicines in the United States Pharmacopoeia (USP) were derived from plants. Today, approximately 20-30% of the drugs listed in USP Dictionary are plant-derived. Important examples include atropine, colchicin, digoxin, and many antineoplastic agents.

Herbal medicines have been dispensed for centuries by traditional herbalists who have been involved with their cultivation and preparation as well as assessment of their potency. At present, most herbal products are commercially

cultivated, processed in unregulated environments, and sold over-the counter without the counseling of a qualified health practitioner.

In this article, descriptions of the following herbal medicines have been mentioned as they are most commonly used.

Commonly used herbal medications

St. John's wort

Ginseng

Garlic

Saw Palmetto

Gingko

Ephedra

Echinacea

Ginger

Kava

Feverfew

Despite many uncertainties in commercial preparations, herbal medications adhere to modern pharmacological principles. A single herbal medication may adversely affect the patient during the perioperative period through a number of different mechanisms. These effects are different (intrinsic pharmacological effects), pharmacodynamic interactions (alteration of the action of conventional drugs at effector sites), and pharmacokinetic interactions (alteration of the absorption, distribution, metabolism, and elimination of conventional drugs).

### POTENTIAL PERIOPERATIVE ANESTHETIC/SYSTEMIC SIDE EFFECTS

Areas of concern to the anaesthesiologist in the perioperative milieu may be of concern where herbal medications are involved :

1. Untoward cardiovascular effects,
2. Enhanced potential for bleeding,
3. Potential for prolongation or interference with anaesthetic agents,
4. Possible renal involvement or hepatotoxicity,
5. Potential for glucose disturbances,
6. Abnormal thyroid function,
7. Risk of decreased effectiveness of HIV protease inhibitors.

### ST. JOHN'S WORT ( HYPERICUM PERFORATUM)

St John's Wort is used in the treatment of mild to moderate depression. Most preparations are standardized to hypericin content (a naphthodianthrone), but recent data indicate that there are other active ingredients as well, including hyperforin. The precise mechanisms of action are not known. Irreversible monoamine oxidase (MAO) inhibitory activity noted in vitro has not been observed in vivo. Other postulated mechanisms include selective inhibition of serotonin,  $\beta$ -amino-butyrates, norepinephrine, and dopamine reuptake in the central nervous system.

Over the past two decades, St. John's Wort has been studied in mild to moderate depression. Most of the clinical trials have shown that it is more effective than placebo and as effective as tricyclic agents for the treatment of mild to moderate depression. St. John's wort also induces the cytochrome P450 system, which may lower the blood levels of other drugs that are metabolized by this system (e.g., ethinyl estradiol, warfarin, cyclosporine, and indinavir). The most affected enzyme appears to be CYP 3A4, which is responsible for the metabolism of more than 50% of conventional medications subject to oxidative metabolism by cytochrome P450. Several cases of cardiac and renal organ rejection have been reported in patients whose previously stable level of cyclosporine was lowered after initiation of St. John's wort. Of further concern is that this herb-drug interaction may persist even after St. John's wort is discontinued.

### ANAESTHETIC IMPLICATIONS

The concomitant use of St. John's Wort is not recommended with photosensitization drugs (e.g., piroxicam, tetracycline), monoamine oxidase inhibitors,  $\beta$ -sympathomimetic amines (e.g., ma – huang, pseudoephedrine hydrochloride), or selective serotonin reuptake inhibitors. There is no data regarding the multitude of potential interactions between anaesthetics and St. John's Wort.

### GARLIC(ALLIUM SATIVUM)

Garlic is one of the most popular herbal remedies and is available in fresh, dried, and powdered forms. Garlic is used for the treatment of hyperlipidemia and atherosclerosis. Allicin, the ingredient believed responsible for garlic's therapeutic benefit and odor, is highly unstable. Both heat and acid destroy the enzyme allinase, which is necessary to produce allicin, and for that reason garlic is best ingested raw. Garlic is also available over-the-counter in multiple

formulations. The best-studied form is an enteric-coated capsule of dehydrated garlic. Freeze-drying helps to retain most of the active ingredients found in raw garlic. Enteric coating permits allicin to be released in the small intestine, thereby enhancing absorption and reducing the breath odor.

Garlic appears to have small effects on cholesterol and very minimal effect of blood pressure and none on glucose levels. The mechanisms of action believed responsible for the lipid-lowering effect include inhibition of HMG-CoA reductase and 14 alpha-demethylase.

In a qualitative review of antithrombotic effects, a modest and short-term effect was identified. Because garlic has some activity against platelet activation, there is theoretical risk of increased bleeding, but there is insufficient evidence to determine a casual association.

Garlic is well tolerated and apparently safe for chronic use. In addition to the well-known breath and body odor, common side effects include gastrointestinal upset, nausea, and flatulence.

A more than 50% reduction in blood levels of saquinavir after garlic supplementation was reported recently. The mechanism of action of this significant herb-drug interaction may be induction of the cytochrome P450 system by the herb, as has been noted also with St. John's wort. Garlic supplementation causes a decrease in platelet aggregation, but the clinical significance of this observation is not clear.

### ANAESTHETIC IMPLICATION

The clinical anaesthesiologist should be aware that garlic may augment the effects of warfarin, heparin, NSAIDs, and aspirin and may result in an abnormal bleeding time, which can lead to an increased risk of intraoperative or postoperative bleeding. In addition, an investigation on the effects of garlic dialysate on diastolic blood pressure (DBP), heart rate (HR), and electrocardiographic (ECG) readings in anaesthetized dogs, and its effects on frequency and tension of isolated rat atria was conducted. The garlic dialysate led to a decrease in DBP and HR in a dose-dependent manner, and the ECG readings revealed a regular sinus bradycardiac rhythm. Furthermore, the addition of garlic dialysate to isolated left rat atria resulted in tension development in a dose-dependent manner. Finally, the results revealed that the positive chronotropism and inotropism induced by the addition of isoproterenol were partially antagonized by preincubation of the rat atria with the garlic dialysate. The investigators concluded that these findings may be explained

by a depressant effect on automaticity and tension development in the heart, thus suggesting a  $\beta$ -adrenergic antagonist action modulated by garlic dialysate.

### GINGKO BILOBA

The dried leaf of the Ginkgo tree has been used medicinally for thousands of years to improve blood flow in a variety of conditions, including memory impairment, dementia, peripheral vascular disease, and tinnitus. The German Commission E has approved a standardized form of ginkgo leaf extract (Egb 761) for the treatment of cognitive impairment and intermittent claudication. Multiple pharmacologically active compounds have been isolated from ginkgo, including flavonoid glycosides and terpine lactones (gingkolides). The flavonoids have antioxidant and free radical scavenging ability. The terpine lactones (especially ginkgolide B) have platelet activating factor antagonist activity. In addition, ginkgo extracts activate certain central neurotransmitters, including the cholinergic system, which may contribute to their beneficial effects on memory and cognition.

In general, ginkgo is well tolerated in healthy adults at recommended doses for up to 6 months. Allergic skin reactions, gastrointestinal disturbances and headache occur in fewer than 2% of patients. There are theoretical concerns about a risk of increased bleeding because antiplatelet activating factor activity has been demonstrated in vitro. Several cases of increased bleeding have been reported (two patients were also taking aspirin or warfarin). Although no bleeding complications have been reported in any clinical trials and causality has not been clearly established. Therefore, caution should be exercised when combining ginkgo with anticoagulants.

### ANAESTHETIC IMPLICATIONS

Concomitant use of ginkgo biloba with aspirin, NSAIDs, warfarin and heparin is not recommended because ginkgo may increase the potential for bleeding in these patients. It would also be appropriate to avoid its concomitant use with anticonvulsant drugs (e.g., carbamazepine, phenytoin, phenobarbital) because ginkgo may decrease the effectiveness of these agents. In addition, it has been recommended that ginkgo should be avoided in patients taking tricyclic antidepressant agents, because it might potentiate the seizure threshold-lowering action of these drugs.

### ECHINACEA

Echinacea ranks among the top-selling herbs in the United States. In 1920s, Echinacea tincture was a popular anti-infective agent until the discovery of antibiotics. Several active ingredients have been identified, including polysaccharides, glycoproteins, alkaloids, and flavonoids. In vitro and animal studies suggest that these ingredients cause stimulation of the immune system (natural killer cells, macrophages, and cytokine activity) and that they possess anti-inflammatory, free radical-scavenging and antiviral activity. There is not sufficient evidence to support the use of Echinacea to prevent upper respiratory tract infection.

In general, Echinacea is well tolerated, with few reported adverse events. Rare allergic reactions have been reported (especially in patient with ragweed allergies). The German Commission E recommends that patients who are pregnant, have autoimmune disease, or who are immuno-compromized should not take Echinacea because of its immune – stimulating effects.

### ANAESTHETIC IMPLICATIONS

The immunostimulatory effects of Echinacea may antagonize the immunosuppressive actions of corticosteroids and cyclosporine. Because the herb can cause inhibition of the hepatic microsomal enzymes, its concomitant use with drugs such as phenytoin, rifampin, and phenobarbitone, which are metabolized by the hepatic microsomal enzymes, should be avoided, because echinacea can precipitate toxicity of these drugs.

### KAVA KAVA(PIPER METHYSTICUM)

Kava is prepared from the dried rhizome of the piper methysticum plant. Traditionally, it was used to prepare a ceremonial drink in the South Pacific Islands. Its present day uses include the treatment of anxiety, stress, and insomnia. The active ingredients (kavapyrones) have central muscle-relaxing properties and anticonvulsant activity. The precise anxiolytic mechanism of action is not fully understood but many involve enhanced binding of gamma-aminobutyric acid in the central nervous system.

Kava has been well tolerated in clinical trials. Fewer than 2 to 3% of patients report gastrointestinal complaints. Kava may have dopamine antagonist properties.

In November 2001, the German government reported 29 cases of hepatitis, cirrhosis, and liver failure possibly associated with the use of kava. Although 18 of these reports were in patients who were also taking medications with

known or potential liver toxicity. As a result, kava products have been taken off the market in Switzerland and Germany. Warnings about possible hepatic toxicity have been issued to patients with acute or chronic liver disease.

### ANAESTHETIC IMPLICATIONS

Antinociceptive effects produced by kava kava may be similar to local anaesthetic responses and appear to be mediated through a non-opiate-dependent pathway. Ethanol can increase the hypnotic effects of kava kava. It should be avoided in patients with endogenous depression and can potentiate the effect of barbiturates and benzodiazepines and cause excessive sedation.

### GINSENG (PANAX GINSENG)

Ginseng root has been used for medical purposes in Asia for over 2000 years. There are three major forms of ginseng in use today. Panax Ginseng known as Asian Ginseng, is commonly used in the United States. Panax quinquefolius, known as American ginseng, is cultivated in the United States and exported to China. Eleutherococcus senticosus, known as Siberian ginseng, is not a member of the panax genus. The German Commission E monograph on ginseng root approves its use as a “tonic to counteract weakness and fatigue, as a restorative for declining stamina and impaired concentration, and as an aid to convalescence”. Extracts are made from dried roots and contain ginsenosides. The mechanisms of action have not been delineated.

Possible drug interactions have been reported between P ginseng and warfarin, calcium channel blockers, digoxin, and alcohol. Earlier reports of “ginseng abuse syndrome” and other toxicities are now attributed to adulterants found in earlier unregulated over-the-counter ginseng products. Indeed, 13 out of 21 ginseng products recently evaluated for quality and purity failed because they contained unacceptable levels of pesticides or heavy metals or inadequate concentrations of ginsenosides.

### ANAESTHETIC IMPLICATIONS

Ginseng should be avoided with patients on anticoagulant medications such as warfarin, heparin, NSAIDs, and aspirin. Because ginseng can cause hypertension, the clinical anaesthesiologist should be focused on clinical consequences of long-term use of this agent. Long-standing hypertension can cause end organ damage, volume depletion, and autonomic instability. Furthermore, because many anaesthetic agents can cause generalized vasodilatory effects, haemodynamic variability can be seen, including

profound intraoperative hypotension. Concomitant use of ginseng with monoamineoxidase inhibitors (e.g., phenelzine sulfate) should be avoided, because manic episodes have been reported with routine use of ginseng. As a result of its potential to exert hypoglycaemic effects, ginseng should be used cautiously in diabetic patients on insulin or oral hypoglycaemic medications. It would therefore follow that the anaesthesiologist would need to have appropriate evaluation of blood glucose levels peri-operatively for applicable patients.

### SAW PALMETTO

Traditionally, the fruit of the dwarf palm tree (*Serenoa repens*) was used by Native Americans for urinary complaints. Saw palmetto is now widely used to treat benign prostatic hyperplasia. In some European countries, herbal medicine is first-line therapy for that problem. The principal active ingredients are sterols and free fatty acids. The mechanism of action is unclear; but there is evidence for inhibition of 5 alpha-reductase activity and dihydrotestosterone binding at the androgen receptor. Two small European studies suggest that the herb is slightly less effective than prazosin and alfuzosin an alpha-adrenergic antagonist.

Adverse reactions to saw palmetto are rare, with occasional reports of mild gastrointestinal symptoms and headaches. Finally, there are few, if any, herbs-drug interactions in the literature regarding this herbal agent. Result of one investigation indicated that recommended doses of saw palmetto are not likely to alter the pharmacokinetics of coadministered medications dependent on the cytochrome P450 isoenzymes CYP 2D6 or CYP 3A4, such as dextromethorphan (CYP 2D6 dependent) and alprazolam (CYP 3A4 dependent).

### ANAESTHETIC IMPLICATION

Although no detailed studies have been done with regard to the anaesthetic interactions, caution should be used if the patient is using benzodiazepines (e.g. alprazolam) or medications such as dextromethorphan because saw palmetto can alter pharmacokinetics of these medications. Elaborate clinical trials on anaesthetic-herb interactions are warranted.

### EPHEDRA ()

The dried young stems of *Ephedra sinica* have been used for thousands of years in traditional Oriental medicine to treat respiratory disorders, especially bronchospasm and

congestion. Ephedra is widely marketed for its stimulant and appetite suppressant effects (alone or in combination with caffeine-like herbs). Ephedra's alkaloids are structurally similar to amphetamines. Sympathomimetic side effects include tremors, severe hypertension, seizures, and arrhythmias. These may lead to myocardial infarction, stroke, and death. The FDA has advised patients with hypertension, glaucoma, seizure disorders, and coronary artery disease to avoid using this product. It is contraindicated also in patients with anxiety, mania, or thyroid disease and in those taking other stimulants or who are pregnant. Because it may increase steroid clearance, it may reduce the effectiveness of prednisone.

### ANAESTHETIC IMPLICATION

The use of ephedrine –containing over-the-counter products is highly relevant to the perioperative period. The possibility of hypertension causing myocardial ischaemia or stroke needs to be considered. Ephedra can potentially interact with volatile general anaesthetic agents (e.g., halothane, isoflurane, desflurane) and cardiac glycosides (e.g., digitalis) to cause cardiac dysrhythmias. Patients taking ephedra for prolonged periods of time can deplete peripheral catecholamine stores. Thus, under general anaesthesia, these patients can potentially have profound intraoperative hypotension, which can be controlled with a direct vasoconstrictor (e.g., phenylephrine) instead of ephedrine. Use of ephedra with phenelzine or other monoamine oxidase inhibitors may result in insomnia, headache, and tremulousness. Concomitant use with oxytocin has been shown to cause hypertension.

### GINGER (ZINGIBER OFFICINALE)

Ginger has been used for the treatment of nausea, vomiting, motion sickness, and vertigo. Western herbalists believe it is useful for healing respiratory ailments. It helps to relieve nasal congestion, sore throats, and decrease headaches and body aches.

Regarding the effects of ginger on coagulation, it has exhibited potent inhibition of thromboxine synthetase. Such inhibition in activity results in a prolonged bleeding time. Study reports indicated that, ginger compounds and derivatives are more potent antiplatelet agents than aspirin under conditions employed in the study. Specifically, paradol, a natural constituent of ginger, was identified as the most potent antiplatelet aggregation agent and cyclooxygenase – 1 inhibitor.

Side effects of ginger include bleeding abnormalities and its use is contraindicated in patients with coagulation dysfunction or those on anticoagulant medications such as NSAIDs, aspirin, heparin, and warfarin.

**ANAESTHETIC IMPLICATIONS**

Ginger may increase bleeding risk, therefore, its use should be avoided in patients on anticoagulants like warfarin and heparin or drugs such as NSAIDs and aspirin. Furthermore, ginger enhance barbiturate effects, and, as a result of an inotropic effect, interfere with cardiac medication therapy. Large quantities of ginger may also cause cardiac arrhythmias and central nervous system depression.

**FEVERFEW (TANACETUM PARTHENIUM)**

The herbal agent feverfew is used to treat headache and fever, prevent migraines and treat menstrual abnormalities. The word is derived from the Latin word ‘febrifugia’, which means “fever reducer”. Although feverfew is commonly used for migraine headaches, the literature is not conclusive with regard to its conclusiveness. Like most herbal compounds, analysis of feverfew-based products have yielded significant variations in the parthenolide contents, a proposed active ingredient between feverfew products.

Feverfew has demonstrated inhibition of serotonin release from aggregating platelets. This mechanism may be related to the inhibition of arachidonic acid release via a phospholipase pathway. Furthermore, feverfew has effectively decreased 86% to 88% of prostaglandin production without exhibiting inhibition of cyclooxygenase.

Adverse reactions to feverfew include aphthous ulcers, abdominal pain, flatulence, nausea, vomiting, and rebound headache with an abrupt stoppage of the herb. As with many herbal agents, feverfew is not recommended in the paediatric population or pregnant or nursing patients. Finally, a condition known as “post feverfew syndrome” can occur in chronic users of feverfew and manifests as anxiety, headaches, insomnia, arthralgias, muscle and joint stiffness, and fatigue.

**ANAESTHETIC IMPLICATIONS**

Because feverfew can inhibit platelet activity, it is reasonable to avoid the concomitant use of this herb in patients taking medications such as heparin, warfarin, NSAIDs, aspirin, and vitamin E. For patients with perioperative bleeding abnormalities, the use of feverfew should be considered in the differential diagnosis. Furthermore, tannin-containing herbs like feverfew can

interact with iron preparations, thereby reducing the bioavailability of such preparations.

**Figure 1**

Table : Common Herbal Medications and Anaesthetic Considerations

Herbal Medication	Anaesthetic Considerations
Echinacea	May potentiate barbiturate toxicity; Possible renal involvement or hepatotoxicity.
Ephedra	May interact with volatile anaesthetics i.e., halothane, and cause ? fatal cardiac dysrhythmias. Profound intraoperative hypotension controlled with phenylephrine and not pseudoephedrine.
Garlic	Increased risk of intraoperative bleeding; Risk of decreased effectiveness of HIV protease inhibitors; Abnormal thyroid function.
Gingko biloba	Increased intraoperative and postoperative bleeding tendencies; May decrease effectiveness of intravenous barbiturates; May cause glucose disturbances; Causes untoward cardiovascular effects.
Ginseng	Increased risk of intraoperative haemodynamic instability; Causes untoward cardiovascular effects; Enhances bleeding potential; Potential for prolongation or interference with anaesthetic agents; Potential for glucose disturbances, abnormal thyroid functions and risk of decreased effectiveness of HIV protease inhibitors.
Kava kava	May potentiate the effect of barbiturates/benzodiazepines, thereby resulting in excessive sedation.
St John's Wort	Pseudoephedrine, MAOIs should be avoided; Potential for prolongation or interference with anaesthetic agents. Risk of decreased effectiveness of HIV protease inhibitors
Ginger	Increased risk of intraoperative haemodynamic instability
Feverfew	Increased risk of intraoperative bleeding, discontinue 2 to 3 weeks before surgery.
Saw palmetto	Untoward cardiovascular effects and enhanced bleeding potentials

**HERBAL MEDICATIONS AND SPINAL AXIS ANAESTHESIA**

Many of the herbal agents are alleged to increase bleeding and may put patients at risk if they are going to undergo regional anaesthesia. The implicated agents are feverfew, garlic, ginger, gingko, and ginseng.

However, there is absolutely no direct evidence in the literature that there is a risk of spinal/ epidural haematoma formation if feverfew, garlic, gingko, or ginseng are not stopped several days before the placement of spinal or epidural blockade. But, there is only indirect evidence that there is a risk of spinal / epidural haematoma formation in patients who continue to take herbal medications and undergo either spinal or epidural anaesthesia. All of these patients may have developed the reported bleeding complication even if they were not taking the herbal agents in question.

**CONCLUSION**

Advertisement explosions in the newspapers, magazines and

television have interested people towards herbal medicines. It is assumed by the users that the medicines made from herbal origin do not cause any harm and thus, they never inform the anaesthesiologists during the preanaesthetic checkup about the herbal medicines they are taking. Therefore, asking patients about self-care and treatment used outside the hospital is an important part of the patient history. The anaesthesiologists should have a detailed knowledge and understanding of the potential risks and purported benefits of herbal medicines. As demonstrated in the article, the use of herbal compounds may alter heart rate, respiratory rate, and the pharmacokinetics of various medications. Such medications may include chosen anaesthetics employed during the stages of anaesthesia. The American Society of Anesthesiologists (ASA), suggests that all herbal medications should be discontinued 2 to 3 weeks before an elective surgical procedure. If the patient is not sure of the contents of the herbal medicine, he or she should be urged to bring the container so that the anaesthesiologist can review the contents of the herbs or preparation. Anaesthetic care in emergency setting should be based on thorough drug-intake history from the patient or a relative, if possible.

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