Preoperative Considerations: Which Herbal Products Should Be Discontinued Before Surgery?

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The term "dietary supplement" has been defined by the Food and Drug Administration (FDA) as any product taken orally that contains an ingredient intended to supplement the diet.[1] Therefore, dietary supplements may contain vitamins, minerals, herbs, amino acids, enzymes, and organ tissues, as well as metabolites, extracts, or concentrates of these substances. Dietary supplements constitute a rapidly growing sector of the US healthcare industry; $17.8 billion was spent on these products in the United States in 2001 alone, of which $4.2 billion was accounted for by herbal remedies.[2] A 380% increase in the use of herbal products was reported between 1990 and 1997 in the United States.[3]

This relatively recent resurgence of interest in herbals has been attributed to the high cost of traditional western medicine, ready accessibility of botanical products, increased exposure to other cultures, and the desire for greater individual control over healthcare.[4] Growth of this segment of the healthcare marketplace prompted the National Institutes of Health to establish the Office of Alternative Medicine in 1992, with a mandate to evaluate the efficacy of alternative therapies.

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Medicinal herbs have been used since the beginning of recorded time.[5] Approximately one quarter of prescription drugs on the market today are still derived from plant products (eg, digoxin from the foxglove plant).[6] The danger inherent in the current widespread use of herbal products is the assumption that the term "natural" is synonymous with "safe."

Demographic Data

More than one third of the US population uses some form of alternative medical therapy, with 70% of the post–baby boom cohort reporting lifetime usage.[3,7] Ten percent of US adults ingested herbal medicine in 1999.[8] Persons most likely to utilize botanicals include white people, those suffering from chronic illnesses, people of higher socioeconomic and educational status, and women.[8] The incidence of alternative medicine supplement use in presurgical patients has been estimated to range from 7% in pregnant women[9] to 39% in patients awaiting elective noncardiac surgery.[10,11] The most frequently used herbals in this population, along with their common names and indications for use have been summarized in Table 1.[12-14]

Regulation

For many years, herbal manufacturers argued that botanicals should be considered "food" for regulatory purposes, whereas the FDA adopted the stance that they should be identified as "drugs" based on the manufacturers' claims of therapeutic

Table 1 Herbal products commonly used by preoperative patients, presented in descending order of frequency[12-14]

Herbal product	Common name(s)	Associated indication(s)
Gingko	Maidenhair tree, kew tree, ginkyo, Japanese silver apricot, salisburia	Dementia, memory loss, tinnitus, cerebrovascular insufficiency, antioxidant, dizziness, antidepressant-induced sexual dysfunction
Garlic	Ajo, allium, stinking rose, rust treacle, nectar of the gods, camphor of the poor, poor man's treacle	Hypertension, hyperlipidemia, antibacterial, prevention of atherosclerosis and cancer, diabetes, allergies, arthritis
Ginseng	Panax, red berry, ren shen, sang	Stress, diabetes, facilitation of learning and memory, stimulant, diuretic
St John's wort	Amber, klamath weed, amber touch-and-heal, goatweed, rosin rose, millepertuis, hypericum, tipton weed	Depression, dysthymia, anxiety, menopausal symptoms, treatment of viral and bacterial infections
Echinacea	American coneflower, black susan, black sampson, comb flower, hedgehog, Indian head, Kansas snakeroot, purple coneflower, red sunflower, scurvy root, snakeroot	Immunostimulant, prevention of the common cold, sunburn, yeast and bacterial infections, migraine
Saw palmetto	Serenoa repens, Sabal, American dwarf palm tree, cabbage palm, fan palm ,scrub palm	Benign prostatic hyperplasia, diuretic, sedative, anti-inflammatory, aphrodisiac
Ephedra	Ma-huang, herbal ecstasy, sea grape, yellow horse, desert herb, yellow astringent, joint fir, squaw tea, Mormon tea, popotillo, teamster's tea	Weight loss, enhancement of athletic ability, relief of nasal congestion, edema, headache
Valerian root	Baldrian, radix valerianae, valeriana	Insomnia, sleep disorders, anxiety, migraine
Kava	Ava, ava pepper, gea, gi, intoxicating long pepper, Kava kava, kavain, kawa, maori kava, malohu, maluk, sakau, tonga, yagona	Anxiety, stress, insomnia, restlessness

efficacy. Overwhelming consumer advocacy resulted in enactment of the Dietary Supplement and Health Education Act (DSHEA) in 1994. The DSHEA created the new category of "dietary supplements," which exempts these products from the rigorous safety and efficacy testing required by the FDA of all prescription and over-the-counter drug products.[15] Manufacturers and distributors may now market any herbal or botanical product without prior approval by the FDA as long as the label does not claim effectiveness for the treatment or prevention of a specific disease and there is a disclaimer stating that the FDA has not evaluated the product. The manufacturer alone is responsible for quality control, yet the burden of proof regarding safety issues lies with the FDA.

Since passage of the DSHEA, serious concerns have been raised regarding the quality and standardization of herbal products, the potential for adulteration, the lack of a reliable postmarketing surveillance reporting system, and the paucity of information regarding herb and drug interactions.[2,16] Although many products are safe, 2621 adverse events associated with dietary supplements, including 101 deaths, were reported to the FDA over a 5-year period.[17]

Implications for Surgical Patients

Direct health risks associated with herbal remedies include recognized pharmacological effects (such as hypertension secondary to licorice or ephedra use), unexpected allergic reactions, toxicity secondary to adulterants, and the very real potential for untoward drug-herb interactions (Table 2).[18] Morbidity secondary to botanical product use may be more prevalent in the perioperative period simply because of multiple drug use and increased physiological susceptibility to adverse effects.[24]

The reluctance of patients to report dietary supplement use to their physicians further complicates the problem; in one study, more than 70% of presurgical patients failed to disclose their use of such products during routine preoperative assessment.[25] Reasons for failing to disclose herbal usage may include (1) a belief that because such products

Table 2 Established drug-herb interactions of particular concern to surgical patients[5,12,13,19-23]

Drug or drug class	Herb(s)	Effect
Anesthetics	Kava, hawthorn, St John's wort, valerian	Excessive sedation and delayed emergence from general anesthesia
	Sarsaparilla	Increases elimination of hypnotics
Antiarrhythmics	Aconite	Potential for aconite-induced ventricular arrhythmias
Antidepressants	St John's wort	Believed to increase serotonin levels, which could lead to serotonin syndrome if used in combination with other serotonergic agents
Antidiabetic agents	Garlic	Causes hypoglycemia
	Ephedra (ma-huang)	Causes hyperglycemia
Antihypertensives	Black cohosh, hawthorn	May potentiate hypotensive effects
	Ephedra (ma-huang), guarana (caffeine)	May cause hypertension and excess sympathetic nervous system stimulation
	Licorice	May cause hypertension
	Yerba maté (Paraguay tea)	May cause hypertension or hypotension and excess sympathetic nervous system stimulation
Barbiturates	Kava, hawthorn	Excessive sedation
	Sarsaparilla	Increases elimination of hypnotics
	St John's wort	Decreases barbiturate-induced sleep time
	Valerian	Prolongs barbiturate-induced sleep time
	DHEA	Increases triazolam levels
Benzodiazepines	Kava, hawthorn, valerian	Excessive sedation
	Sarsaparilla	Increases elimination of hypnotics
Corticosteroids	Echinacea, licorice, alfalfa sprouts	Immunostimulant effect of herbs may offset immunosuppressant action of corticosteroids
Cyclosporine	Echinacea, licorice, alfalfa sprouts	Immunostimulant effect of herbs may offset immunosuppressant action of cyclosporine
	St John's wort	May reduce cyclosporine levels
Digoxin	Hawthorn	Potentiates digoxin
	Licorice	May cause hypokalemia, making the patient more vulnerable to digoxin toxicity
	Plantain	Herb may be adulterated with foxglove, resulting in elevated digoxin levels
	Ginseng	May cause falsely elevated digoxin assay or elevated digoxin levels
	Aloe	May potentiate digoxin toxicity
	Sarsaparilla (Smilax species only)	Increases digoxin absorption
	St John's wort	Decreases digoxin levels
Diuretics	Ginseng	Decreases diuretic effects
	Aloe	May potentiate effect of thiazides
GERD agents (proton pump inhibitors, histamine-2 antagonists, antacids)	Peppermint	Reduces lower esophageal sphincter pressure, worsening GERD and hiatal hernia symptoms
Warfarin	Feverfew, ginger, ginkgo, horse chestnut, pau d'arco, danshen, dong quai, fenugreek, garlic, saw palmetto, vitamin E	May increase anticoagulant effects of warfarin, resulting in bleeding complications
	Alfalfa, ginseng, green tea, St John's wort, ubiquinone (coenzyme Q10)	May decrease anticoagulant effects of warfarin

are "natural" they must be entirely safe—a point of view heartily endorsed by many herbal manufacturers, (2) fear of how healthcare providers would respond to self-medication, and (3) fear that their physician may be prejudiced against use of botanicals.[24]

Adverse effects of particular concern for patients undergoing anesthesia include cardiac instability and electrolyte disturbances, prolonged bleeding, and excessive sedation.[14] These effects will be discussed in detail, highlighting the herbal products implicated.

Cardiac Instability

Cardiovascular effects of anesthetic agents include decreased myocardial contractility and vascular smooth muscle tone, resulting in vasodilation, hypotension, and decreased cardiac output.[26] Further, anesthetics delivered by inhalation may sensitize the myocardium to the proarrhythmic effects of other drugs (such as epinephrine) and botanicals (such as ephedra).[26] Thus, herbal products with blood pressure altering or arrhythmogenic potential should be avoided in patients undergoing surgical procedures.

A significant amount of data has been accumulated to date regarding the cardiovascular and cerebrovascular adverse events associated with ephedra alkaloids (Figure 1).[27,28] Ephedra (also known as ma-huang) is a common ingredient in many herbal weight loss and energy-booster products, and is often packaged in combination with guarana (caffeine). Table 3 lists the brand names of several popular combination herbal products marketed as weight loss or metabolic enhancers that contain both ephedra and guarana extracts. Ephedra use has been linked to hypertension, palpitations, tachycardia, seizures, stroke, heart attack, and sudden death even in patients with no underlying heart or vascular disease.[27,28] Although some deaths have been associated with excessive use, other patients died after consuming ephedra within the manufacturer's recommended guidelines for use.[27] Ephedra has been identified as the herbal product with the greatest potential for harm in perioperative patients.[14] Increased regulation of this herbal product may occur in the near future, particularly given the relatively simple chemical conversion of ephedra into methamphetamine, a street drug with enormous destructive potential. An FDA press release recommends that individuals with hypertension, heart conditions, and neurologic disorders should avoid using ephedra.[29]

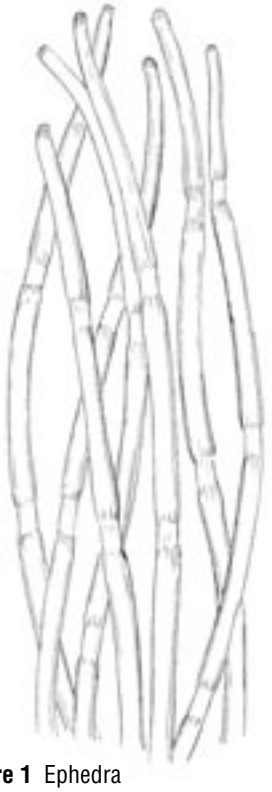

Figure 1 Ephedra

Table 3 Ephedra and guarana contents of popular combination herbal agents marketed as herbal weight loss products or metabolic enhancers[13]

Brand name	Manufacturer	Ephedra (ma-huang) content, mg	Guarana (caffeine) content, mg
Diet Fuel	Twin Lab	334 (extract)	909 (extract)
Diet Metabo	Source Naturals	30 (ephedrine alkaloids)	100 (caffeine)
Hydroxycut	Muscletech	334 (extract)	910 (extract)
Metabolife 356	Metabolife	12 (naturally occurring ephedrines)	40 (caffeine)
Ripped Fuel	Twin Lab	20	200
Ripped Fuel Metabolic Enhancer	Twin Lab	334 (extract)	910 (extract)
Thermic Blast	Human Development Technologies	335 (extract)	910 (extract)
Thermicore	Met-Rx	250 (extract)	200 caffeine
Thermo Cuts	Optimum Nutrition	334 (extract)	910 (extract)
Thermo Trim	Swanson	334 (extract)	909 (extract)
Xenadrine RFA-1	Cytodyne Technologies	335 (extract)	910 (extract)
Xtreme Trim	Puritan's Pride	335 (extract)	910 (extract)

Note: Only the ephedra and guarana contents have been listed here; each of these products is a multi-ingredient preparation containing 5 to 20 different herbs and extracts. Ephedra and guarana contents have been listed exactly as cited. Ma-huang extracts generally contain approximately 6% ephedra alkaloids by weight. Guarana extracts are 22% caffeine by weight.

Other herbal products that have been documented to elevate blood pressure include guarana (caffeine) and licorice.[12,13] Yerba maté (Paraguay tea) may cause either hypertension or hypotension.[12,13] Licorice has been categorized as unsafe based on documentation of pseudoaldosteronism (manifested by sodium and water retention, hypertension, heart failure, and cardiac arrest) in patients who used the herb in high dosages for long periods.[30]

Aconite (also known as monkshood, friar's cap, helmet flower, or wolfsbane) is a botanical product that has been used to treat pain. Use of this herb has been documented to cause ventricular arrhythmias unresponsive to procainamide, as well as complete cardiovascular collapse.[12] Its use should be strictly contraindicated in patients who are to receive anesthesia, particularly inhaled anesthetics.

Prolonged Bleeding

Herbals that may alter coagulation either via pharmacokinetic interaction with warfarin or secondary to inherent antiplatelet or anticoagulant effects include feverfew, ginger, ginkgo, horse chestnut, pau d'arco, danshen, dong quai, fenugreek, garlic, and saw palmetto (Table 2).[12,13,23] Case reports documenting postoperative bleeding complications have implicated danshen and gingko.[23]

Ginkgo (Figure 2) is also believed to have been responsible for causing a spontaneous hyphema in a 70-year-old man who had ingested 40 mg of concentrated ginkgo extract twice daily in combination with 325 mg of aspirin daily for 1 week,[31] bilateral subdural hematomas in a 33-year-old woman after ingestion of 60 mg of ginkgo twice daily for 2 years,[32] and a frontal subdural hematoma in a 72-year-old woman after consumption of 50 mg ginkgo 3 times daily for 6 months.[33]

Figure 2 Ginkgo

Garlic (Figure 3) is thought to have been the cause of a spontaneous epidural hematoma in an elderly man who ingested approximately 2000 mg of garlic daily for an unspecified period.[34] Garlic consumption in this case was excessive (the equivalent of 4 cloves daily). Regular ingestion of garlic-containing foods is not believed to pose any risk.[23]

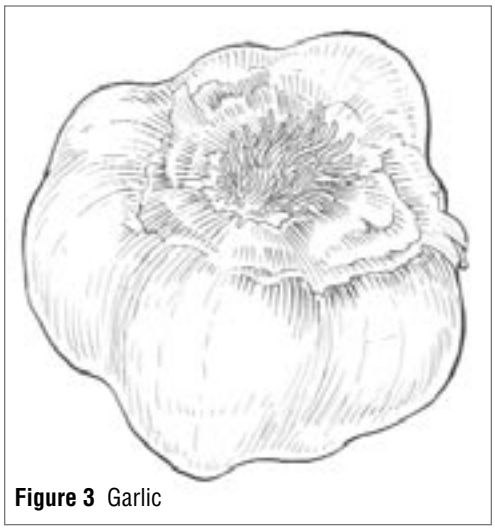

Figure 3 Garlic

Botanical products documented to increase international normalized ratios (INRs) in patients taking warfarin as an anticoagulant include danshen (the root of the *Salvia miltiorrhiza* plant), dong quai (a Chinese supplement gaining popularity in the United States), and papain (proteolytic enzymes from the fruit of the papaya tree).[23] Conversely, a decrease in INRs has been reported for patients taking warfarin in combination with coenzyme Q10 (ubiquinone), Oriental ginseng, and green tea.[23] Although the mechanism for the procoagulant effect of ginseng (Figure 4) remains a mystery, it is known that dried green tea leaves contain substantial amounts of vitamin K and that coenzyme Q10 is structurally related to vitamin K_2.[23] Thus, increased ingestion of vitamin K is the likely explanation for their mechanism of warfarin antagonism.

Herbs believed to contain coumarin or coumarin derivatives include angelica root, arnica flower, anise, celery, chamomile, fenugreek, horse chestnut, licorice, lovage root, parsley, passionflower herb, quassia, red clover, and rue.[23] Antiplatelet activity has been reported for turmeric, clove, onion, and bromelain, whereas willow bark, poplar, and meadowsweet contain high concentrations of salicylates.[12,13] These herbal products should be considered theoreti-

Figure 4 Ginseng

cal risks for prolonged bleeding at this point. Until more information becomes available, it would be wise to discourage use of any of these herbs in patients taking warfarin or who are undergoing any type of surgical procedure.

Excessive Sedation

Any herb with inherent sedative properties has the potential to delay emergence from anesthesia. Sedative herbs include kava (Figure 5), hawthorn, and St John's wort.[12,13] Kava (also known as kava kava or *Piper methysticum*) is a popular anxiolytic that has come under fire recently by the FDA because of multiple reports of hepatotoxicity.[35] There is a single case report of an interaction between kava and alprazolam that purportedly resulted in a semicomatose state.[36] Further, kava is believed to have additive effects with benzodiazepines based on a similar mechanism of action on γ-aminobutyric acid receptors in the brain.[36]

St John's wort (Figure 6) is an herb commonly used for depression. Evidence suggests that one of the alkaloids in St John's wort may be a monoamine oxidase inhibitor (MAOI). There are no contraindications with use of MAOIs and inhaled anesthetics (eg, halothane)[37]; however, there is concern that concomitant administration of MAOIs with narcotics may result in hypotension and exaggeration of the respiratory and central nervous system depressant effects of the narcotic.[38] Thus, St John's wort should be discontinued before surgical procedures in which narcotic analgesia is anticipated.

Valerian (Figure 7) is a popular herb used as a sleep aid and anxiolytic. An extract of valerian containing valerenic acid has been shown to prolong barbiturate-induced sleeping time.[39] Valerenic acid is an inhibitor of γ-aminobutyric acid transaminase, thereby contributing to valerian's sedative properties. Although generally considered as safe by the FDA as a food additive, caution is warranted because of the potential for excessive sedation when surgical patients consume valerian.

Figure 5 Kava

Figure 6 St John's wort

Figure 7 Valerian

Conclusion

A significant percentage of surgical patients use dietary supplements on a regular basis, yet many are reluctant to reveal this fact to their healthcare providers. Caregivers should be aware of the many potential adverse

effects that herbal products may have on patients undergoing surgery, including excessive sedation, increased risk of bleeding, and cardiac instability. It is extremely important for healthcare professionals to take an accurate, nonjudgmental, and thorough history of all medication use, including herbals. This screening should be a routine part of preanesthetic assessment, and should occur far enough in advance to allow for discontinuation of potentially dangerous botanical products with relatively long half-lives.

The American Society of Anesthesiologists offers no official guidelines regarding the perioperative use of herbals. However, educational materials released by this organization encourage patients to

Table 4 Perioperative concerns of herbal products commonly utilized by surgical patients and recommended time for discontinuation prior to surgery

Herbal product	Surgical/anesthetic consideration	Recommended time for discontinuation before procedure
Ephedra (ma-huang)	Cardiac instability secondary to ephedra's propensity to cause hypertension, heart attack, palpitations, vasoconstriction and sudden cardiac death[27,28]	At least 1 day[24]
Garlic	May cause prolonged bleeding	At least 1 week[24]
Ginkgo	May cause prolonged bleeding	At least 1 1/2 days[24]
Ginseng	Hypotension and possible procoagulant effect	At least 1 week[24]
Guarana (caffeine)	Hypertension	At least 1 day[42]
Kava	Excessive sedation and potential for delayed emergence from anesthesia	At least 1 day[24]
Licorice	Hypertension and potential pseudoaldosteronism via glycyrrhizin component	At least 1 day[43]
St John's wort	Excessive sedation and delayed emergence from general anesthesia	At least 5 days[24]
Valerian	Excessive sedation and potential for delayed emergence from anesthesia	At least 1 week[44]

Table 5 Internet resources for reliable information on herbal products

Sponsoring organization	URL	Description
Natural Medicines Comprehensive Database	http://www.naturaldatabase.com	Arguably the best comprehensive resource on herbals and supplements, published by the *Pharmacist's Letter.* Has an excellent appendix summarizing drug-herb interactions. Requires a subscription.
Facts and Comparisons, Review of Natural Products	http://www.factsandcomparisons.com	Excellent comprehensive guide to herbal products. Extensively referenced. Excellent evidence-based drug-herb interaction table. Requires a subscription
FDA Center for Food Safety and Applied Nutrition	http://www.cfsan.fda.gov/~dms/supplmnt.html	Basic overview of dietary supplements, definitions, regulations
FDA Center for Food Safety and Applied Nutrition	http://www.cfsan.fda.gov/~dms/ds-warn.html	Adverse event warnings and safety information
FDA Center for Food Safety and Applied Nutrition	http://www.cfsan.fda.gov/~dms/ds-rept.html	Provides link to FDA adverse event reporting form
National Institutes of Health, Office of Dietary Supplements	http://dietary-supplements.info.nih.gov	Health information, fact sheets on supplements
National Center for Alternative and Complementary Medicine	http://nccam.nih.gov/health	Treatment information organized by supplement and by disease or condition
National Library of Medicine and National Institutes of Health	http://www.nlm.nih.gov/medlineplus/alternativemedicine.html	Health information, definitions, latest news, clinical trial updates
National Institutes of Health	http://clinicaltrials.gov/search/intervention+alternative+medicine&recruiting=true	Future and ongoing clinical trial information; recruitment information for patients who want to be involved

discontinue their herbal products at least 2 to 3 weeks before surgery.[40] Hodges and Kam[41] have made a blanket recommendation that all botanicals should be stopped 2 weeks before surgery.

Although discontinuation of herbals 2 to 3 weeks before any surgical procedure is an admirable goal, it may not be practical in all cases. Ang-Lee et al[24] have emphasized the utilization of half-lives (the time required for 50% of any substance to be removed from the body, whether this occurs via renal clearance or hepatic metabolism) to determine the recommended discontinuation period. If this value has been determined for the active ingredient in an herbal product, then a good estimate for discontinuation time would be the half-life multiplied by 5. After 5 half-lives, the amount of any compound left in the body will be approximately 3% of the original serum concentration—a quantity unlikely to cause harm. Table 4 summarizes discontinuation recommendations for those herbs utilized commonly in presurgical patients. If a botanical product of concern does not appear in this table, it may be concluded that the half-life and/or the active ingredient remain unknown, and the default discontinuation recommendation should be at least 2 weeks before surgery.[26,39]

The field of herbal medicine is rapidly evolving. Unfortunately, the Internet often provides as much misinformation as information regarding these substances. Trustworthy sources of information concerning herbal products and dietary supplements have been compiled in Table 5, with associated commentary regarding the content and usefulness of each site.

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