# Herbal Medicines and Perioperative Care

Michael K. Ang-Lee, MD
Jonathan Moss, MD, PhD
Chun-Su Yuan, MD, PhD

**Context** Widespread use of herbal medications among the presurgical population may have a negative impact on perioperative patient care.

**Objectives** To review the literature on commonly used herbal medications in the context of the perioperative period and provide rational strategies for managing their preoperative use.

**Data Sources** The MEDLINE and Cochrane Collaboration databases were searched for articles published between January 1966 and December 2000 using the search terms *herbal medicine*, *phytotherapy*, and *alternative medicine* and the names of the 16 most commonly used herbal medications. Additional data sources were obtained from manual searches of recent journal articles and textbooks.

**Study Selection** We selected studies, case reports, and reviews addressing the safety and pharmacology of 8 commonly used herbal medications for which safety information pertinent to the perioperative period was available.

**Data Extraction** We extracted safety, pharmacodynamic, and pharmacokinetic information from the selected literature and reached consensus about any discrepancies.

**Data Synthesis** Echinacea, ephedra, garlic, ginkgo, ginseng, kava, St John's wort, and valerian are commonly used herbal medications that may pose a concern during the perioperative period. Complications can arise from these herbs' direct and pharmacodynamic or pharmacokinetic effects. Direct effects include bleeding from garlic, ginkgo, and ginseng; cardiovascular instability from ephedra; and hypoglycemia from ginseng. Pharmacodynamic herb-drug interactions include potentiation of the sedative effect of anesthetics by kava and valerian. Pharmacokinetic herb-drug interactions include increased metabolism of many drugs used in the perioperative period by St John's wort.

**Conclusions** During the preoperative evaluation, physicians should explicitly elicit and document a history of herbal medication use. Physicians should be familiar with the potential perioperative effects of the commonly used herbal medications to prevent, recognize, and treat potentially serious problems associated with their use and discontinuation.

*JAMA. 2001;286:208-216* www.jama.com

THERE IS ENORMOUS PUBLIC ENthusiasm for herbal medications. Two recent surveys have found widespread use among the presurgical population.[1,2] Morbidity and mortality associated with herbal medications may be more likely in the perioperative period because of the polypharmacy and physiological alterations that occur.[3] Such complications include myocardial infarction, stroke, bleeding, inadequate oral anticoagulation, prolonged or inadequate anesthesia, organ transplant rejection, and interference with medications indispensable for patient care.

Of the herbal medications that clinicians are likely to encounter, we have identified 8 of the herbs that potentially pose the greatest impact to the care of patients undergoing surgery. These herbs account for more than 50% of all single herb preparations among the 1500 to 1800 herbal medications sold in the United States.[4,5] Nonherbal dietary supplements, such as vitamins, minerals, amino acids, and hormones, are beyond the scope of this review. Some of these nonherbal dietary supplements that patients undergoing surgery are most likely to take, such as glucosamine and chondroitin for osteoarthritis,[6,7] appear to be safe. Limited information is available, however, on the use of these supplements in the presurgical population.

In this article, we consider safety and US regulatory issues for herbal medications; review the literature on the identified 8 commonly used herbal medications as they affect perioperative care; and propose rational strategies for managing the preoperative use of these agents. The prevention, recognition, and treatment of complications begin with explicitly eliciting and documenting a history of herbal medicine use. Familiarity with the scientific literature on herbal medications is necessary because the current US regulatory mechanism for commercial herbal preparations sold in the United States does not necessarily protect the population against unpredictable or undesirable effects. Our goal is to provide a framework for physicians practicing in the contemporary environment where widespread herbal medicine use occurs.

**Author Affiliations:** Department of Anesthesia and Critical Care (Drs Ang-Lee, Moss, and Yuan), Tang Center for Herbal Medicine Research (Dr Yuan), and Committee on Clinical Pharmacology (Dr Yuan), The Pritzker School of Medicine, University of Chicago, Chicago, Ill.
**Corresponding Author and Reprints:** Chun-Su Yuan, MD, PhD, Department of Anesthesia and Critical Care, University of Chicago, 5841 S Maryland Ave, MC 4028, Chicago, IL 60637 (e-mail: cyuan@midway.uchicago.edu).

### Preoperative Use of Herbal Medications

The most extensive surveys on the use of complementary and alternative medicine use in the United States revealed that approximately 12% of the population used herbal medications in 1997,[8,9] representing a 380% increase from 1990. Patients undergoing surgery appear to use herbal medications significantly more frequently than the general population. For instance, Tsen et al[1] reported that 22% of patients who underwent evaluation in their preoperative clinic took herbal medications. Also, Kaye et al[2] found that 32% of patients in an ambulatory surgery setting admitted to using herbal medications.

More than 70% of the patients in the study by Kaye et al[2] failed to disclose their herbal medicine use during routine preoperative assessment. Explanations for this lack of disclosure include patient-held beliefs that physicians are not knowledgable about herbal medications or are prejudiced against their use.[10] Some patients may fear admitting to their physicians their use of unconventional therapies.[11] Others may neglect to mention that they are taking herbal medications when they are using them for reasons perceived as unrelated to their medical care.[12] Still other patients would not consider these substances to be medications, and they may neglect to report them during routine preoperative questioning. For these reasons, it is necessary for physicians to specifically seek out a history of herbal medicine use in presurgical patients.

### Regulation and Safety of Herbal Medications

Herbal medications were classified as dietary supplements in the Dietary Supplement Health and Education Act of 1994.[13] This law exempts herbal medications from the safety and efficacy requirements and regulations that prescription and over-the-counter drugs must fulfill (ie, preclinical animal studies, premarketing controlled clinical trials, or postmarketing surveillance). The burden is shifted to the US Food and Drug Administration to show that a product is unsafe before it can be removed from the market.[14] In addition, the inability to patent herbal medications discourages the manufacturers from performing the costly research required for conventional drugs.[15]

The current US regulatory mechanism provides little assurance that commercial herbal preparations have predictable pharmacological effects and that product labels provide accurate information. The potency of herbal medications can vary from manufacturer to manufacturer and from lot to lot within a manufacturer.[16-18] Plants may be misidentified or deliberately replaced with cheaper or more readily available alternatives.[19-22] Moreover, herbal medications, especially those of Eastern origin, can be adulterated with heavy metals, pesticides, and even conventional drugs.[23-25] Some herbal manufacturers have tried to standardize their herbal products to fixed concentrations of selected chemical constituents.[26] The benefit of this effort is uncertain, however, because many products achieve their effects through the combined or synergistic actions of different compounds.[27] Even when advertised and labeled as standardized, potency can still vary considerably.[28]

Because there is no mechanism for postmarketing surveillance, the incidence and exact nature of adverse events is unknown. Empirical evidence gained from a long history of herbal medication use supports the notion that most are safe.[29] Nevertheless, some of these medications have been associated with serious harm.[30,31] More than 5000 suspected herb-related adverse reactions were reported to the World Health Organization before 1996.[32] Between January 1993 and October 1998, 2621 adverse events, including 101 deaths, associated with dietary supplements were reported to the US Food and Drug Administration.[33] However, adverse events are underreported because there is no central mechanism for mandatory reporting as there is for conventional medications. Other factors that contribute to underreporting are that physicians do not always recognize adverse events associated with herbal medication use[34] and that patients are reluctant to report and seek treatment for the adverse reactions.[35] This reluctance has been attributed to the belief that physicians cannot be consulted in the use of unconventional therapies and that patients are unwilling to admit the use of these remedies to physicians. The deficiencies in monitoring adverse events for herbal medicines mean that safety profiles are usually limited to animal studies, case reports, or predictions derived from known pharmacological results.

## METHODS

We identified the most commonly used herbal medications by 1999 sales data and surveys in the literature.[1,2,4] The MEDLINE and Cochrane Collaboration databases were searched for articles published between January 1966 and December 2000, using the search terms *herbal medicine*, *phytotherapy*, *alternative medicine*, and the names of the most commonly used herbal medications (*aloe*, *bilberry*, *cascara*, *cranberry*, *echinacea*, *ephedra*, *garlic*, *ginseng*, *ginkgo*, *goldenseal*, *kava*, *milk thistle*, *saw palmetto*, *soy*, *St John's wort*, and *valerian*). Additional sources included manual searches of textbooks and recent surgery, anesthesiology, and alternative medicine journals.

Although we found no randomized controlled trials that evaluated the effects of prior herbal medicine use on the perioperative period, we identified, based on our judgments, those studies, case reports, and reviews addressing the safety, pharmacokinetics, and pharmacodynamics of the commonly used herbs that may affect the care of these patients.

## RESULTS

### Eight Commonly Used Herbal Medications

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 direct (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).

### Echinacea

Three species of echinacea, a member of the daisy family, are used for the prophylaxis and treatment of viral, bacterial, and fungal infections, particularly those of the upper respiratory tract.[36] Pharmacological activity cannot be attributed to a single compound, although the lipophilic fraction, which contains the alkylamides, polyacetylenes, and essential oils, appears to be more active than the hydrophilic fraction.

Preclinical studies of echinacea have shown a number of immunostimulatory effects.[37-39] While no studies specifically addressing interactions between echinacea and immunosuppressive drugs have been conducted, expert opinion generally warns against the concomitant use of echinacea and these drugs because of the probability of diminished effectiveness.[37,40,41] Therefore, patients who may require perioperative immunosuppression, such as those awaiting organ transplantion, should be counseled to avoid taking echinacea. In contrast to the immunostimulatory effects with short-term use, long-term use of longer than 8 weeks is accompanied by the potential for immunosuppression[41] and a theoretically increased risk of certain postsurgical complications, such as poor wound healing and opportunistic infections.

Echinacea also has been associated with allergic reactions, including 1 reported case of anaphylaxis.[42] Thus, echinacea should be used with caution in patients with asthma, atopy, or allergic rhinitis. In addition, concerns of potential hepatoxicity have been raised, although documented cases are lacking.[17] Because of the absence of definitive information, patients with preexisting liver dysfunction should be cautious when taking echinacea. Furthermore, since the pharmacokinetics of echinacea have not been studied, it may be prudent for patients to discontinue taking echinacea as far in advance of surgery as possible when compromises in hepatic function or blood flow are anticipated. These situations often occur secondary to concomitant anesthetic drug administration or as an effect of surgical manipulation.

### Ephedra

Ephedra, known as ma huang in Chinese medicine, is a shrub native to central Asia. It is used to promote weight loss, increase energy, and treat respiratory tract conditions, such as asthma and bronchitis. Ephedra contains alkaloids, including ephedrine, pseudoephedrine, norephedrine, methylephedrine, and norpseudoephedrine.[43] Commercial preparations may be standardized to a fixed ephedrine content.

Ephedra causes dose-dependent increases in blood pressure and heart rate. Ephedrine, the predominant active compound, is a noncatecholamine sympathomimetic agent that exhibits $\alpha_1$, $\beta_1$, and $\beta_2$ activity by acting directly at adrenergic receptors and by indirectly releasing endogenous norepinephrine. These sympathomimetic effects have been associated with more than 1070 reported adverse events, including fatal cardiac and central nervous system complications.[44]

Although ephedrine is widely used as first-line therapy for intraoperative hypotension and bradycardia, the unsupervised preoperative use of ephedra raises certain concerns. Vasoconstriction and, in some cases, vasospasm of coronary and cerebral arteries may cause myocardial infarction and thrombotic stroke.[45] Patients who have consumed ephedra and are later anesthetized with halothane may be at risk of developing intraoperative ventricular arrhythmias because halothane sensitizes the myocardium to ventricular arrhythmias caused by exogenous catacholamines.[46] Ephedra also may affect cardiovascular function by causing hypersensitivity myocarditis, characterized by cardiomyopathy with myocardial lymphocyte and eosinophil infiltration.[47] Long-term use results in tachyphylaxis from depletion of endogenous catecholamine stores and may contribute to perioperative hemodynamic instability. In these situations, direct-acting sympathomimetic agents may be preferred as first-line therapy for intraoperative hypotension and bradycardia. Concomitant use of ephedra and monoamine oxidase inhibitors can result in life-threatening hyperpyrexia, hypertension, and coma. Finally, heavy use of ephedra has been documented as a very rare cause of radiolucent kidney stones.[48,49]

The pharmacokinetics of ephedrine have been studied in humans.[50,51] Ephedrine has an elimination half-life of 5.2 hours with 70% to 80% of the compound excreted unchanged in urine. Based on the pharmacokinetic data and the known cardiovascular risks of ephedra, including myocardial infarction, stroke, and cardiovascular collapse from catecholamine depletion, patients taking this herb should discontinue use at least 24 hours prior to surgery.

### Garlic

Garlic is one of the most extensively researched medicinal plants. It has the potential to modify the risk of developing atherosclerosis by reducing blood pressure and thrombus formation and lowering serum lipid and cholesterol levels.[52] These effects are primarily attributed to the sulfur-containing compounds, particularly allicin and its transformation products. Commercial garlic preparations may be standardized to a fixed alliin and allicin content.

Garlic inhibits platelet aggregation in a dose-dependent fashion. The effect of 1 of its constituents, ajoene, appears to be irreversible and may potentiate the effect of other platelet inhibitors, such as prostacyclin, forskolin, indomethacin, and dipyridamole.[53,54] Although these effects have not been consistently demonstrated in volunteers, there

is one case in the literature of an octogenarian who developed a spontaneous epidural hematoma that was attributed to heavy use of garlic.[55] In addition to concerns about bleeding, garlic has the potential to lower blood pressure. In laboratory animals, allicin decreased systemic and pulmonary vascular resistance[56] and lowered blood pressure.[57] In humans, however, the antihypertensive effect of garlic is marginal.[58]

Although there are insufficient pharmacokinetic data of the constituents of garlic, the potential for irreversible inhibition of platelet function may warrant patients to discontinue use of garlic at least 7 days prior to surgery, especially if postoperative bleeding is a particular concern or other platelet inhibitors are given.

### Ginkgo

Ginkgo is derived from the leaf of *Ginkgo biloba*. It has been used for cognitive disorders, peripheral vascular disease, age-related macular degeneration, vertigo, tinnitus, erectile dysfunction, and altitude sickness. Studies suggest that ginkgo may stabilize or improve cognitive performance in patients with Alzheimer disease and multi-infarct dementia.[59,60] The compounds believed to be responsible for its pharmacological effects are the terpenoids and flavonoids. The 2 ginkgo extracts used in clinical trials are standardized to ginkgo-flavone glycosides and terpenoids.

Ginkgo appears to alter vasoregulation,[61] act as an antioxidant,[62] modulate neurotransmitter and receptor activity,[63] and inhibit platelet-activating factor.[64] Of these effects, the inhibition of platelet-activating factor raises the greatest concern for the perioperative period since platelet function may be altered. Clinical trials with small numbers of patients have not demonstrated complications from bleeding, but 4 cases of spontaneous intracranial bleeding,[65-68] 1 case of spontaneous hyphema,[69] and 1 case of postoperative bleeding following laparoscopic cholecystectomy[70] have been attributed to ginkgo use.

Terpenoids are highly bioavailable when administered orally. Glucuronidation appears to be part of the metabolism of the flavonoids.[71] The elimination half-lives of the terpenoids after oral administration are between 3 and 10 hours.[72] Based on the pharmacokinetic data and the risk of bleeding, particularly in the surgical population, patients should discontinue taking ginkgo at least 36 hours prior to surgery.

### Ginseng

Among the several species used for pharmacologic effects, Asian ginseng and American ginseng are the most commonly described. Ginseng has been labeled as an "adaptogen," since it reputedly protects the body against stress and restores homeostasis.[73] Most pharmacological actions are attributed to the ginsenosides that belong to a group of compounds known as *steroidal saponins*. Commercially available ginseng preparations may be standardized to ginsenoside content.

Ginseng has a broad but incompletely understood pharmacological profile because of the many heterogeneous and sometimes opposing effects of different ginsenosides.[74] The underlying mechanism appears to be similar to that classically described for steroid hormones. A potential therapeutic use for this herb has to do with its ability to lower postprandial blood glucose in both patients with type 2 diabetetes mellitus and without diabetes,[75] but this effect may create unintended hypoglycemia, particularly in patients who have fasted before surgery. There is a concern about the effect of ginseng on coagulation pathways. Ginsenosides inhibit platelet aggregation in vitro[76,77] and in laboratory rats, prolong both coagulation time of thrombin and activated partial thromboplastin.[78] One early study suggests that the antiplatelet activity of panaxynol, a constituent of ginseng, may be irreversible in humans.[79] These findings await further confirmation. Although ginseng may inhibit the coagulation cascade, ginseng use was associated with a significant decrease in warfarin anticoagulation in 1 reported case.[80]

The pharmacokinetics of ginsenosides $Rg_1$, Re, and $Rb_2$ have been investigated in rabbits, with elimination half-lives between 0.8 and 7.4 hours.[81] These data suggest that patients should discontinue ginseng use at least 24 hours prior to surgery. However, because platelet inhibition caused by ginseng may be irreversible, it is probably prudent to recommend that patients discontinue ginseng use at least 7 days prior to surgery.

### Kava

Kava is derived from the dried root of the pepper plant *Piper methysticum*. Kava has gained widespread popularity as an anxiolytic and sedative. Results from clinical trials suggest that kava has a therapeutic potential in the symptomatic treatment of anxiety.[82] The kavalactones appear to be the source of the pharmacological activity of kava.[83]

Because of its psychomotor effects, kava was one of the first herbal medications expected to interact with anesthetics. The kavalactones have dose-dependent effects on the central nervous system, including antiepileptic,[84] neuroprotective,[85] and local anesthetic properties.[84] Kava may act as a sedative-hypnotic by potentiating γ-aminobutyric acid (GABA) inhibitory neurotransmission. The kavalactones increased barbiturate-induced sleep time in laboratory animals.[86] This effect may explain the mechanism underlying the report of a case of coma attributed to an alprazolam-kava interaction.[87] Although kava has abuse potential, whether long-term use can result in addiction, tolerance, and acute withdrawal after abstinence has not been satisfactorily investigated. With heavy use, kava produces a condition called *kava dermopathy*, characterized by reversible scaly cutaneous eruptions.[88]

Peak plasma levels occur 1.8 hours after an oral dose, and the elimination half-life of kavalactones is 9 hours.[83] Unchanged kavalactones and their metabolites are eliminated through urine and feces.[89] The pharmacokinetic data and possibility for the potentiation of the sedative effects of anesthetics sug-

gest that patients taking kava should discontinue use at least 24 hours prior to surgery.

### St John's Wort

St John's wort is the common name for *Hypericum perforatum*. A number of clinical trials have reported efficacy in the short-term treatment of mild-to-moderate depression.[90] However, a recent multicenter clinical trial concluded that St John's wort is not effective in the treatment of major depression.[91] The compounds believed to be responsible for pharmacological activity are hypericin and hyperforin.[92] Commercial preparations are often standardized to a fixed hypericin content of 0.3%.

St John's wort exerts its effects by inhibiting serotonin, norepinephrine, and dopamine reuptake by neurons.[93,94] Concomitant use of this herb with or without serotonin-reuptake inhibitors may create a syndrome of central serotonin excess.[95,96] Although early in vitro data implicated monoamine oxidase inhibition as a possible mechanism of action,[97] a number of further investigations have demonstrated that monoamine oxidase inhibition is insignificant in vivo.[98,99]

The use of St John's wort can significantly increase the metabolism of many concomitantly administered drugs, some of which are vital to the perioperative care of certain patients. For example, the cytochrome isoform P450 3A4 is induced, approximately doubling its metabolic activity.[100,101] Interactions with substrates of the P450 3A4 isoform, including indinavir sulfate,[102] ethinyl estradiol,[103] and cyclosporin, have been documented. In 1 series of 45 organ transplant recipients, St John's wort was associated with a mean decrease of 49% in blood cyclosporine levels.[104] Another study reported 2 cases of acute heart transplant rejection associated with this particular pharmacokinetic interaction.[105] Other P450 3A4 substrates commonly used in the perioperative period include alfentanil, midazolam hydrochloride, lidocaine, calcium channel blockers, and serotonin receptor antagonists. In addition to the P450 3A4 isoform, the cytochrome isoform P450 2C9 also may be induced. In 7 reported cases, the anticoagulant effect of warfarin, a substrate of the P450 2C9 isoform, was reduced.[103] Other P450 2C9 substrates include the nonsteroidal anti-inflammatory drugs. Furthermore, the enzyme induction caused by St John's wort may be more pronounced when other enzyme inducers, which could include other herbal medications, are taken concomitantly. St John's wort also affects digoxin pharmacokinetics, possibly by inducing the P-glycoprotein transporter.[106]

In humans, the single-dose and steady-state pharmacokinetics of hypericin, pseudohypericin, and hyperforin have been determined.[107,108] After oral administration, peak plasma levels of hypericin and hyperforin were obtained in 6.0 and 3.5 hours, and their median elimination half-lives of were 43.1 and 9.0 hours, respectively. The long half-life and alterations in the metabolism of many drugs make concomitant use of St John's wort a particular risk in the perioperative setting. The pharmacokinetic data suggest that patients taking this herbal medication should discontinue use at least 5 days prior to surgery. This discontinuation is especially important for patients waiting for organ transplantation or in those who may require oral anticoagulation postoperatively; thus, these patients should be counseled to avoid taking St John's wort postoperatively.

### Valerian

Valerian is an herb native to the temperate areas of the Americas, Europe, and Asia. It is used as a sedative, particularly in the treatment of insomnia, and virtually all herbal sleep aids contain valerian.[109] Valerian contains many compounds acting synergistically, but the sesquiterpenes are the primary source of the pharmacological effects of valerian. Commercially available preparations may be standardized to valerenic acid.

Valerian produces dose-dependent sedation and hypnosis.[110] These effects appear to be mediated through modulation of GABA neurotransmission and receptor function.[111,112] In experimental animals, valerian increases barbiturate-induced sleep time.[113] In 1 patient, valerian withdrawal appeared to mimic an acute benzodiazepine withdrawal syndrome after the patient presented with delirium and cardiac complications following surgery and the patient's symptoms were attenuated by benzodiazepine administration.[114] Based on these findings, valerian should be expected to potentiate the sedative effects of anesthetics and adjuvants, such as midazolam, that act at the GABA receptor.

The pharmacokinetics of the constituents of valerian have not been studied, although their effects are thought to be short-lived. 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. In these individuals, with close medical supervision, it may be prudent to taper the dose of valerian during several weeks before surgery. If this is not feasible, physicians can advise patients to continue taking valerian up until the day of surgery. Based on the mechanism of action and a reported case of efficacy,[114] benzodiazepines can be used to treat withdrawal symptoms should they develop during the postoperative period.

## COMMENT

Because most patients may not volunteer that they are taking herbal medications in the preoperative evaluation,[2] physicians should specifically elicit and document a history of herbal medication use. Obtaining such a history may be difficult. Written questionnaires for information on herbal medication use have not shown to be beneficial in identifying patients taking these remedies, since half of patients who use alternate therapies fail to report this information during an evaluation unless they are questioned in person.[115] An oral history, however, also has been shown to be inadequate. Unless this information is directly so-

licited, patients may not be forthcoming. Even when a history of herbal medication use is obtained, 1 of 5 patients is unable to properly identify the preparation they are taking.[116] Therefore, patients should be asked to bring their herbal medications and other dietary supplements with them to their preoperative evaluation.

Patients who use herbal medications may be more likely than those who do not to avoid seeking conventional diagnosis and therapy.[117] Hence, a history of herbal medicine use should prompt physicians to suspect the presence of undiagnosed disorders causing symptoms that may lead to self-medication using herbal remedies. These recommendations also apply to pediatric patients because caretakers may treat children with herbal medications without medical supervision.[118] In 1 survey, 1 in 6 parents reported giving dietary supplements to their children.[10]

Although the American Society of Anesthesiologists has no official standards or guidelines on the preoperative use of herbal medications, public and professional educational information released by this organization suggest that patients discontinue their herbal medications at least 2 to 3 weeks before surgery.[119,120] Our review of the literature favors a more targeted approach. Pharmacokinetic data on selected active constituents indicate that some herbal medications are eliminated quickly and may be discontinued closer to the time of surgery. Tailoring recommendations for preoperative discontinuation of herbal medications may be necessary since evaluating patients 2 to 3 weeks before elective surgery may be impossible in practice. Moreover, some patients require nonelective surgery or are noncompliant with instructions to discontinue herbal medications preoperatively. These factors and the high frequency of herbal medicine use may mean that many patients will take herbal medications until the time of surgery. Therefore, clinicians should be familiar with commonly used herbal medications to recognize and treat complications that may arise. TABLE 1 summarizes the clinically important effects, perioperative concerns, and recommendations for dis-

**Table 1.** Clinically Important Effects and Perioperative Concerns of 8 Herbal Medicines and Recommendations for Discontinuation of Use Before Surgery*

| Herb: Common Name(s) | Relevant Pharmacological Effects | Perioperative Concerns | Preoperative Discontinuation |
|---|---|---|---|
| Echinacea: purple coneflower root | Activation of cell-mediated immunity | Allergic reactions; decreased effectiveness of immunosuppressants; potential for immunosuppression with long-term use | No data |
| Ephedra: ma huang | Increased heart rate and blood pressure through direct and indirect sympathomimetic effects | Risk of myocardial ischemia and stroke from tachycardia and hypertension; ventricular arrhythmias with halothane; long-term use depletes endogenous catecholamines and may cause intraoperative hemodynamic instability; life-threatening interaction with monoamine oxidase inhibitors | At least 24 hours before surgery |
| Garlic: ajo | Inhibition of platelet aggregation (may be irreversible); increased fibrinolysis; equivocal antihypertensive activity | Potential to increase risk of bleeding, especially when combined with other medications that inhibit platelet aggregation | At least 7 days before surgery |
| Ginkgo: duck foot tree, maidenhair tree, silver apricot | Inhibition of platelet-activating factor | Potential to increase risk of bleeding, especially when combined with other medications that inhibit platelet aggregation | At least 36 hours before surgery |
| Ginseng: American ginseng, Asian ginseng, Chinese ginseng, Korean ginseng | Lowers blood glucose; inhibition of platelet aggregation (may be irreversible); increased PT-PTT in animals; many other diverse effects | Hypoglycemia; potential to increase risk of bleeding; potential to decrease anticoagulation effect of warfarin | At least 7 days before surgery |
| Kava: awa, intoxicating pepper, kawa | Sedation, anxiolysis | Potential to increase sedative effect of anesthetics; potential for addiction, tolerance, and withdrawal after abstinence unstudied | At least 24 hours before surgery |
| St John's wort: amber, goat weed, hardhay, Hypericum, klamatheweed | Inhibition of neurotransmitter reuptake, monoamine oxidase inhibition is unlikely | Induction of cytochrome P450 enzymes, affecting cyclosporine, warfarin, steroids, protease inhibitors, and possibly benzodiazepines, calcium channel blockers, and many other drugs; decreased serum digoxin levels | At least 5 days before surgery |
| Valerian: all heal, garden heliotrope, vandal root | Sedation | Potential to increase sedative effect of anesthetics; benzodiazepine-like acute withdrawal; potential to increase anesthetic requirements with long-term use | No data |

*PT-PTT indicates prothrombin time-partial thromboplastin time.

**Table 2.** Herbal Medicine and Other Dietary Supplement–Related Sites on the World Wide Web

| Organization | Web Address | Site Information |
|---|---|---|
| Center for Food Safety and Applied Nutrition, Food and Drug Administration | http://vm.cfsan.fda.gov/~dms/supplmnt.html | Clinicians should use this site to report adverse events associated with herbal medicines and other dietary supplements. Sections also contain safety, industry, and regulatory information. |
| National Center for Complementary and Alternative Medicine, National Institutes of Health | http://nccam.nih.gov | This site contains factsheets about alternative therapies, consensus reports, and databases. |
| Agricultural Research Service, United States Department of Agriculture | http://www.ars-grin.gov/duke | The site contains an extensive phytochemical database with search capabilities. |
| Quackwatch | http://www.quackwatch.com | Although this site addresses all aspects of health care, there is a considerable amount of information covering complementary and herbal therapies. |
| National Council Against Health Fraud | http://www.ncahf.org | This site focuses on health fraud with a position paper on over-the-counter herbal remedies. |
| HerbMed | http://www.herbmed.org | This site contains information on more than 120 herbal medications, with evidence for activity, warnings, preparations, mixtures, and mechanisms of action. There are short summaries of important research publications with MEDLINE links. |
| ConsumerLab | http://www.consumerlab.com | This site is maintained by a corporation that conducts independent laboratory investigations of dietary supplements and other health products. |

continuation of the 8 herbal medications before surgery.

Clinicians also should recognize that discontinuation of all herbal medications before surgery may not free a patient from risks related to their use. Since withdrawal of conventional medications is associated with increased morbidity and mortality after surgery, it is conceivable that withdrawal of herbal medications may be similarly detrimental.[121] In patients with alcoholism, preoperative abstinence of alcohol use may result in poorer postoperative outcome than continued preoperative drinking.[122] The danger of abstinence after long-term use may be similar with herbal medications, such as valerian, which have the potential for producing acute withdrawal after long-term use.

Because the herbal medicine field is rapidly evolving, sources for reliable and updated information are important in helping physicians stay abreast of new discoveries about the effects of herbal medications and other dietary supplements. TABLE 2 lists several resources that are available on the World Wide Web as clinical aides.

In summary, the task of caring perioperatively for patients who use herbal medications is an evolving challenge. The limited evidence-based information about the safety and efficacy of herbal medications, the absence of a standard regulatory mechanism for herbal medicine approval and surveillance, and improper patient assumptions about herbal medications represent important medical issues. Although there has been initiation of herbal medicine into medical school curricula at several institutions many practicing physicians remain unaware of potential perioperative complications of herbal medication use. Physicians should be familiar with all medications, whether conventional or herbal, their patients are taking. This information is necessary to prevent, recognize, and treat potentially serious problems associated with herbal medications, taken alone or in conjunction with conventional medications.

**Author Contributions:** *Study concept and design*: Ang-Lee, Moss, Yuan.
*Aquisition of data*: Ang-Lee, Moss, Yuan.
*Analysis and interpretation of data*: Ang-Lee, Moss, Yuan.
*Drafting of the manuscript*: Ang-Lee.
*Critical revision of the manuscript for important intellectual content*: Ang-Lee, Moss, Yuan.
*Obtained funding*: Moss, Yuan.
*Administrative, technical, or material support*: Ang-Lee, Moss, Yuan.
*Study supervision*: Moss, Yuan.
**Funding/Support:** This work was supported in part by the Tang Family Foundation and Clinical Practice Enhancement and Anesthesia Research Foundation.
**Acknowledgment:** We are indebted to John E. Ellis, MD, and P. Allan Klock, Jr, MD, for their comments on the manuscript and Sally Kozlik for her editorial assistance.

## REFERENCES

**1.** Tsen LC, Segal S, Pothier M, Bader AM. Alternative medicine use in presurgical patients. *Anesthesiology*. 2000;93:148-151.
**2.** Kaye AD, Clarke RC, Sabar R, et al. Herbal medications: current trends in anesthesiology practice–a hospital survey. *J Clin Anesth*. 2000;12:468-471.
**3.** Bovill JG. Adverse drug interactions in anesthesia. *J Clin Anesth*. 1997;9(suppl 6):3S-13S.
**4.** NBJ herbal and botanical U.S. consumer sales. *Nutrition Business Journal*. 2000. Available at: http://www.nutritionbusiness.com. Accessibility verified June 8, 2001.
**5.** Commission on Dietary Supplement Labels. *Report of the Commission on Dietary Supplement Labels, Report to the President, Congress, and The Secretary of the Department of Health and Human Services*. Washington, DC: US Government Printing Office; 1997.
**6.** McAlindon TE, La Valley MP, Gulin JP, Felson DT. Glucosamine and chondroitin for treatment of osteoarthritis. *JAMA*. 2000;283:1469-1475.
**7.** Reginster JY, Deroisy R, Rovati LC, et al. Long-term effects of glucosamine sulphate on osteoarthritis progression: a randomized, placebo-controlled clinical trial. *Lancet*. 2001;357:251-256.
**8.** Eisenberg DM, Davis RB, Ettner SL, et al. Trends in alternative medicine use in the United States, 1990-1997: results of a follow-up study. *JAMA*. 1998;280:1569-1575.
**9.** Eisenberg DM, Kessler RC, Foster C, Norlock FE, Calkins DR, Delbanco TL. Unconventional medicine in the United States: prevalence, costs, and patterns of use. *N Engl J Med*. 1993;328:246-252.
**10.** Blendon RJ, DesRoches CM, Benson JM, Brodie M, Altman DE. American's views on the use and regulation of dietary supplements. *Arch Intern Med*. 2001;161:805-810.
**11.** Eisenberg DM. Advising patients who seek alternative medical therapies. *Ann Intern Med*. 1997;127:61-69.
**12.** Elder NC, Gillcrist A, Minz R. Use of alternative health care by family practice patients. *Arch Fam Med*. 1997;6:181-184.
**13.** Dietary Supplement Health and Education Act, Pub L No. 103-417, 180 Stat 2126 (1994).
**14.** Marwick C. Growing use of medicinal botanicals forces assessment by drug regulators. *JAMA*. 1995;273:607-609.

**15.** Matthews HB, Lucier GW, Fisher KD. Medicinal herbs in the United States: research needs. *Environ Health Perspect*. 1999;107:773-778.
**16.** Winslow LC, Kroll DJ. Herbs as medicines. *Arch Intern Med*. 1998;158:2192-2199.
**17.** Miller LG. Herbal medicinals: selected clinical considerations focusing on known or potential drug-herb interactions. *Arch Intern Med*. 1998;158:2200-2211.
**18.** Herbal roulette. *Consumer Reports*. November 1995:698-705.
**19.** Ernst E. Harmless herbs? a review of the recent literature. *Am J Med*. 1998;104:170-178.
**20.** Slifman NR, Obermeyer WR, Aloi BK, et al. Contamination of botanical dietary supplements by *Digitalis lanata*. *N Engl J Med*. 1998;339:806-811.
**21.** Kessler DA. Cancer and herbs. *N Engl J Med*. 2000; 342:1742-1743.
**22.** Nortier JL, Martinez MC, Schmeiser HH, et al. Urothelial carcinoma associated with the use of a Chinese herb (*Aristolochia fangchi*). *N Engl J Med*. 2000; 342:1686-1692.
**23.** Ko RJ. Adulterants in Asian patent medicines. *N Engl J Med*. 1998;339:847.
**24.** Vander Stricht BI, Parvais OE, Vanhaelen-Fastre RJ, Vanhaelen MH, Quertinier D. Safer use of traditional remedies: remedies may contain cocktail of active drugs. *BMJ*. 1994;308:1162.
**25.** Espinoza EO, Bleasdell B. Arsenic and mercury in traditional Chinese herbal balls. *N Engl J Med*. 1995; 333:803-804.
**26.** Thompson CA. Herbal quality seems to be growing. *Am J Health Syst Pharm*. 1998;55:2341-2342.
**27.** Wagner H. Phytomedicine research in Germany. *Enivron Health Perspect*. 1999;107:779-781.
**28.** Monmaney T. Label's potency claims often inaccurate, analysis finds. *Los Angeles Times*. August 31, 1998:A10.
**29.** Abbot NC, White AR, Ernst E. Complementary medicine. *Nature*. 1996;381:361.
**30.** Windrum P, Hull DR, Morris TCM. Herb-drug interactions. *Lancet*. 2000;355:1019-1020.
**31.** Fugh-Berman A. Herb-drug interactions. *Lancet*. 2000;355:134-138.
**32.** Edwards R. Monitoring the safety of herbal medicine: WHO project is under way. *BMJ*. 1995;311: 1569-1570.
**33.** Herbal Rx—the promises and pitfalls. *Consumer Reports*. March 1999:44-48.
**34.** Perharic L, Shaw D, Murray V. Toxic effects of herbal medications and food supplements. *Lancet*. 1993;342:180-181.
**35.** Barnes J, Mills SY, Abbot NC, Willoughby M, Ernst E. Different standards for reporting ADRs to herbal remedies and conventional OTC medicines: face-to-face interviews with 515 users of herbal remedies. *Br J Clin Pharmacol*. 1998;45:496-500.
**36.** Melchart D, Linde K, Fischer P, Kaesmayr J. *Echinacea for preventing and treating the common cold*. Cochrane Database Syst Rev. 2000;(2):CD000530.
**37.** Pepping J. Echinacea. *Am J Health Syst Pharm*. 1999;56:121-122.
**38.** See DM, Broumand N, Sahl L, Tilles JG. In vitro effects of echinacea and ginseng on natural killer and antibody-dependent cell cytotoxicity in healthy subjects and chronic fatigue syndrome or acquired immunodeficiency syndrome patients. *Immunopharmacology*. 1997;35:229-235.
**39.** Rehman J, Dillow JM, Carter SM, Chou J, Le B, Maisel AS. Increased production of antigen-specific immunoglobulins G and M following in vivo treatment with the medicinal plants *Echinacea angustifolia* and *Hydrastis canadensis*. *Immunol Lett*. 1999;68:391-395.
**40.** Echinacea. In: Gruenwald J, Brendler T, Jaenicke C, eds. *PDR for Herbal Medicines*. 2nd ed. Montvale, NJ: Medical Economics Co; 2000:261-266.
**41.** Boullata JI, Nace AM. Safety issues with herbal medicine. *Pharmacotherapy*. 2000;20:257-269.
**42.** Mullins RJ. Echinacea-associated anaphylaxis. *Med J Aust*. 1998;168:170-171.
**43.** Gurley BJ, Gardner SF, Hubbard MA. Content versus label claims in ephedra-containing dietary supplements. *Am J Health Syst Pharm*. 2000;57:963-969.
**44.** Nightingale SL. From the Food and Drug Administration. *JAMA*. 1997;278:15.
**45.** Haller CA, Benowitz NL. Adverse cardiovascular and central nervous system events associated with dietary supplements containing ephedra alkaloids. *N Engl J Med*. 2000;343:1833-1838.
**46.** Roizen MF. Anesthetic implications of concurrent diseases. In: Miller RD, ed. *Anesthesia*. 4th ed. New York, NY: Churchill Livingstone Inc; 1994:903-1014.
**47.** Zaacks SM, Klein L, Tan CD, Rodriguez ER, Leikin JB. Hypersensitivity myocarditis associated with ephedra use. *J Toxicol Clin Toxicol*. 1999;37:485-489.
**48.** Blau JJ. Ephedrine nephrolithiasis associated with chronic ephedrine abuse. *J Urol*. 1998;160:825.
**49.** Powell T, Hsu FF, Turk J, Hruska K. Ma-huang strikes again: ephedrine nephrolithiasis. *Am J Kidney Dis*. 1998;32:153-159.
**50.** White LM, Gardner SF, Gurley BJ, Marx MA, Wang PL, Estes M. Pharmacokinetics and cardiovascular effects of ma-huang (*Ephedra sinica*) in normotensive adults. *J Clin Pharmacol*. 1997;37:116-122.
**51.** Gurley BJ. Gardner SF, White LM, Wang PL. Ephedrine pharmacokinetics after the ingestion of nutritional supplements containing *Ephedra sinica* (ma huang). *Ther Drug Monit*. 1998;20:439-445.
**52.** Stevinson C, Pittler MH, Ernst E. Garlic for treating hypercholesterolemia: a meta-analysis of randomized clinical trials. *Ann Intern Med*. 2000;133:420-429.
**53.** Srivastava KC. Evidence for the mechanism by which garlic inhibits platelet aggregation. *Prostaglandins Leukot Med*. 1986;22:313-321.
**54.** Apitz-Castro R, Escalante J, Vargas R, Jain MK. Ajoene, the antiplatelet principle of garlic, synergistically potentiates the antiaggregatory action of prostacyclin, forskolin, indomethacin and dypiridamole on human platelets. *Thromb Res*. 1986;42:303-311.
**55.** Rose KD, Croissant PD, Parliament CF, Levin MB. Spontaneous spinal epidural hematoma with associated platelet dysfunction from excessive garlic ingestion: a case report. *Neurosurgery*. 1990:26:880-882.
**56.** Kaye AD, De Witt BJ, Anwar M, et al. Analysis of responses of garlic derivatives in the pulmonary valscular bed of the rat. *J Appl Physiol*. 2000;89:353-358.
**57.** Ali M, Al-Qattan KK, Al-Enezi F, Khanafer RM, Mustafa T. Effect of allicin from garlic powder on serum lipids and blood pressure in rats fed with a high cholesterol diet. *Prostaglandins Leukot Essent Fatty Acids*. 2000;62:253-259.
**58.** Silagy CA, Neil HA. A meta-analysis of the effect of garlic on blood pressure. *J Hypertens*. 1994;12: 463-468.
**59.** Le Bars PL, Katz MM, Berman N, Itil TM, Freedman AM, Schatzberg AF. A placebo-controlled, double-blind, randomized trial of an extract of *Ginkgo biloba* for dementia: North American EGb Study Group. *JAMA*. 1997;278:1327-1332.
**60.** Oken BS, Storzbach DM, Kaye JA. The efficacy of *Ginkgo biloba* on cognitive function in Alzheimer disease. *Arch Neurol*. 1998;55:1409-1415.
**61.** Jung F, Mrowietz C, Kiesewetter H, Wenzel E. Effect of *Ginkgo biloba* on fluidity of blood and peripheral microcirculation in volunteers. *Arzneimittelforschung*. 1990;40:589-593.
**62.** Maitra I, Marcocci L, Droy-Lefaix MT, Packer L. Peroxyl radical scavenging activity of *Ginkgo biloba* extract EGb 761. *Biochem Pharmacol*. 1995;49:1649-1655.
**63.** Hoyer S, Lannert H, Noldner M, Chatterjee SS. Damaged neuronal energy metabolism and behavior are improved by *Ginkgo biloba* extract (EGb 761). *J Neural Transm*. 1999;106:1171-1188.
**64.** Chung KF, Dent G, McCusker M, Guinot P, Page CP, Barnes PJ. Effect of a ginkgolide mixture (BN 52063) in antagonizing skin and platelet responses to platelet activating factor in man. *Lancet*. 1987;1:248-251.
**65.** Rowin J, Lewis SL. Spontaneous bilateral subdural hematomas associated with chronic *Ginkgo biloba* ingestion. *Neurology*. 1996;46:1775-1776.
**66.** Vale S. Subarachnoid haemorrhage associated with *Ginkgo biloba*. *Lancet*. 1998;352:36.
**67.** Gilbert GJ. *Ginkgo biloba*. *Neurology*. 1997;48: 1137.
**68.** Matthews MK Jr. Association of *Ginkgo biloba* with intracerebral hemorrhage. *Neurology*. 1998;50: 1933-1934.
**69.** Rosenblatt M, Mindel J. Spontaneous hyphema associated with ingestion of *Ginkgo biloba* extract. *N Engl J Med*. 1997;336:1108.
**70.** Fessenden JM, Wittenborn W, Clarke L. *Gingko biloba*: a case report of herbal medicine and bleeding postoperatively from a laparoscopic cholecystectomy. *Am Surg*. 2001;67:33-35.
**71.** Watson DG, Oliveira EJ. Solid-phase extraction and gas chromatography—mass spectrometry determination of kaempferol and quercetin in human urine after consumption of *Ginkgo biloba* tablets. *J Chromatogr B Biomed Sci Appl*. 1999;723:203-210.
**72.** Ginkgo. In: Mills S, Bone K, eds. *Principles and Practice of Phytotherapy*. New York, NY: Churchill Livingstone Inc; 2000:404-417.
**73.** Brekham II, Dardymov IV. New substances of plant origin which increase nonspecific resistance. *Annu Rev Pharmacol*. 1969;9:419-430.
**74.** Attele AS, Wu JA, Yuan CS. Ginseng pharmacology: multiple constituents and multiple actions. *Biochem Pharmacol*. 1999;58:1685-1693.
**75.** Vuksan V, Sievenpiper JL, Koo VY, et al. American ginseng (*Panax quinquefolius L*) reduces postprandial glycemia in nondiabetic subjects and subjects with type 2 diabetes mellitus. *Arch Intern Med*. 2000;160:1009-1013.
**76.** Kimura Y, Okuda H, Arichi S. Effects of various ginseng saponins on 5-hydroxytryptamine release and aggregation in human platelets. *J Pharm Pharmacol*. 1988;40:838-843.
**77.** Kuo SC, Teng CM, Lee JC, Ko FN, Chen SC, Wu TS. Antiplatelet components in *Panax ginseng*. *Planta Med*. 1990;56:164-167.
**78.** Park HJ, Lee JH, Song YB, Park KH. Effects of dietary supplementation of lipophilic fraction from *Panax ginseng* on cGMP and cAMP in rat platelets and on blood coagulation. *Biol Pharm Bull*. 1996;19:1434-1439.
**79.** Teng CM, Kuo SC, Ko FN, et al. Antiplatelet actions of panaxynol and ginsenosides isolated from ginseng. *Biochim Biophys Acta*. 1989;990:315-320.
**80.** Janetzky K, Morreale AP. Probable interaction between warfarin and ginseng. *Am J Health Syst Pharm*. 1997;54:692-693.
**81.** Chen SE, Sawchuk RJ, Staba EJ. American ginseng: III, pharmacokinetics of ginsenosides in the rabbit. *Eur J Drug Metab Pharmacokinet*. 1980;5:161-168.
**82.** Pittler MH, Ernst E. Efficacy of kava extract for treating anxiety: systematic review and meta-analysis. *J Clin Psychopharmacol*. 2000;20:84-89.
**83.** Pepping J. Kava: *Piper methysticum*. *Am J Health Syst Pharm*. 1999;56:957-958, 960.
**84.** Meyer HJ. Pharmacology of kava.1. *Psychopharmacol Bull*. 1967;4:10-11.
**85.** Backhauss C, Krieglstein J. Extract of kava (*Piper methysticum*) and its methysticin constituents protect brain tissue against ischemic damage in rodents. *Eur J Pharmacol*. 1992;215:265-269.
**86.** Jamieson DD, Duffield PH, Cheng D, Duffield AM. Comparison of the central nervous system activity of the aqueous and lipid extract of kava (*Piper methysticum*). *Arch Int Pharmacodyn Ther*. 1989; 301:66-80.
**87.** Almeida JC, Grimsley EW. Coma from the health

food store: interaction between kava and alprazolam. *Ann Intern Med*. 1996;125:940-941.
**88.** Norton SA, Ruze P. Kava dermopathy. *J Am Acad Dermatol*. 1994;31:89-97.
**89.** Rasmussen AK, Scheline RR, Solheim E, Hansel R. Metabolism of some kava pyrones in the rat. *Xenobiotica*. 1979;9:1-16.
**90.** Gaster B, Holroyd J. St John's wort for depression: a systematic review. *Arch Intern Med*. 2000; 160:152-156.
**91.** Shelton RC, Keller MB, Gelenberg A, et al. Effectiveness of St John's wort in major depression. *JAMA*. 2001;285:1978-1986.
**92.** Muller WE, Singer A, Wonnemann M, Hafner U, Rolli M, Schafer C. Hyperforin represents the neurotransmitter reuptake inhibiting constituent of hypericum extract. *Pharmacopsychiatry*. 1998;31(suppl 1):16-21.
**93.** Neary JT, Bu Y. Hypericum LI 160 inhibits uptake of serotonin and norepinephrine in astrocytes. *Brain Res*. 1999;816:358-363.
**94.** Franklin M, Chi J, McGavin C, et al. Neuroendocrine evidence for dopaminergic actions of hypericum extract (LI 160) in healthy volunteers. *Biol Psychiatry*. 1999;46:581-584.
**95.** Lantz MS, Buchalter E, Giambanco V. St. John's wort and antidepressant drug interactions in the elderly. *J Geriatr Psychiatry Neurol*. 1999;12:7-10.
**96.** Brown TM. Acute St. John's wort toxicity. *Am J Emerg Med*. 2000;18:231-232.
**97.** Suzuki O, Katsumata Y, Oya M, Bladt S, Wagner H. Inhibition of monoamine oxidase by hypericin. *Planta Med*. 1984;50:272-274.
**98.** Yu PH. Effect of the *Hypericum perforatum* extract on serotonin turnover in the mouse brain. *Pharmacopsychiatry*. 2000;33:60-65.
**99.** Muller WE, Rolli M, Schafer C, Hafner U. Effects of hypericum extract (LI 160) in biochemical models of antidepressant activity. *Pharmacopsychiatry*. 1997; 30(suppl 2):102-107.
**100.** Obach RS. Inhibition of human cytochrome P450 enzymes by constituents of St. John's wort, an herbal preparation used in the treatment of depression. *J Pharmacol Exp Ther*. 2000;294:88-95.
**101.** Ernst E. Second thoughts about safety of St. John's wort. *Lancet*. 1999;354:2014-2016.
**102.** Piscitelli SC, Burstein AH, Chaitt D, Alfaro RM, Falloon J. Indinavir concentrations and St. John's wort. *Lancet*. 2000;355:547-548.
**103.** Yue QY, Bergquist C, Gerden B. Safety of St. John's wort. *Lancet*. 2000;355:576-577.
**104.** Breidenbach T, Hoffmann MW, Becker T, Schlitt H, Klempnauer J. Drug interaction of St. John's wort with cyclosporin. *Lancet*. 2000;355:1912.
**105.** Ruschitzka F, Meier PJ, Turina M, Luscher TF, Noll G. Acute heart transplant rejection due to Saint John's wort. *Lancet*. 2000;355:548-549.
**106.** Johne A, Brockmoller J, Bauer S, Maurer A, Langheinrich M, Roots I. Pharmacokinetic interaction of digoxin with an herbal extract from St. John's wort (*Hypericum perforatum*). *Clin Pharmacol Ther*. 1999;66: 338-345.
**107.** Kerb R, Brockmoller J, Staffeldt B, Ploch M, Roots I. Single-dose and steady-state pharmacokinetics of hypericin and pseudohypericin. *Antimicrob Agents Chemother*. 1996;40:2087-2093.
**108.** Biber A, Fischer H, Romer A, Chatterjee SS. Oral bioavailability of hyperforin from hypericum extracts in rats and human volunteers. *Pharmacopsychiatry*. 1998;31(suppl 1):36-43.
**109.** Houghton PJ. The scientific basis for the reputed activity of valerian. *J Pharm Pharmacol*. 1999; 51:505-512.
**110.** Hendriks H, Bos R, Allersma DP, Malingre TM, Koster AS. Pharmacological screening of valerenal and some other components of essential oil of *Valeriana officinalis*. *Planta Med*. 1981;42:62-68.
**111.** Ortiz JG, Nieves-Natal J, Chavez P. Effects of *Valeriana officinalis* extracts on [$^3$H] flunitrazepam binding, synaptosomal [$^3$H]GABA uptake, and hippocampal [$^3$H]GABA release. *Neurochem Res*. 1999;24:1373-1378.
**112.** Santos MS, Ferreira F, Cunha AP, Carvalho AP, Ribeiro CF, Macedo T. Synaptosomal GABA release as influenced by valerian root extract—involvement of the GABA carrier. *Arch Int Pharmacodyn Ther*. 1994; 327:220-231.
**113.** Leuschner J, Muller J, Rudmann M. Characterization of the central nervous depressant activity of a commercially available valerian root extract. *Arzneimittelforschung*. 1993;43:638-641.
**114.** Garges HP, Varia I, Doraiswamy PM. Cardiac complications and delirium associated with valerian root withdrawal. *JAMA*. 1998;280:1566-1567.
**115.** Hensrud DD, Engle DD, Scheitel SM. Underreporting the use of dietary supplements and nonprescription medications among patients undergoing a periodic health examination. *Mayo Clin Proc*. 1999; 74:443-447.
**116.** Kassler WJ, Blanc P, Greenblatt R. The use of medicinal herbs by human immunodeficiency virus-infected patients. *Arch Intern Med*. 1991;151:2281-2288.
**117.** Cirigliano M, Sun A. Advising patients about herbal therapies. *JAMA*. 1998;280:1565-1566.
**118.** Coppes MJ, Anderson RA, Egeler RM, Wolff JEA. Alternative therapies for the treatment of childhood cancer. *N Engl J Med*. 1998;339:846-847.
**119.** Leak JA. Herbal medicines: what do we need to know? *ASA Newsletter*. 2000:64.
**120.** Anesthesiologists warn: if you're taking herbal products, tell your doctor before surgery. Available at: http://www.asahq.org/PublicEduction/herbal.html. Accessed May 10, 2001.
**121.** Kennedy JM, van Rij AM, Spears GF, Pettigrew RA, Tucker IG. Polypharmacy in a general surgical unit and consequences of drug withdrawal. *Br J Clin Pharmacol*. 2000;49:353-362.
**122.** Tonnesen H, Rosenberg J, Nielsen HJ, et al. Effect of preoperative abstinence on poor postoperative outcome in alcohol misusers: randomized controlled trial. *BMJ*. 1999;318:1311-1316.

The shrewd guess, the fertile hypothesis, the courageous leap to a tentative conclusion—these are the most valuable coin of the thinker at work.
—Jerome Seymour Bruner (1915- )