

HERBAL MEDICINES AND INTERACTIONS WITH ANESTHETIC AGENTS

ELIZABETH A.M. FROST*

Introduction

Herbs and related products are commonly used by patients who also seek conventional health care. All physicians, regardless of specialty, care for patients who use products that are neither prescribed nor recommended. More than 20,000 herbal and related products are presently available in the United States¹. Since a complete review of specific herbs would be monumental, the potential benefits and hazards only of the more popular herbal products are described. As many as 70% of patients do not reveal their use of these agents to treating physicians, considering nutraceuticals as “natural supplements” rather than a form of medicine^{2,3}. Hence, the patient presenting to the hospital for emergency or elective surgery may pose a considerable challenge for healthcare professionals in terms of unexpected complications during perioperative care.

Definition and Use of Herbs

Herbs are derived from flowers, shrubs, trees, algae, ferns, fungi, seaweeds and grasses. They are used not only to treat diseases but to improve the quality of life. All parts of plants are used. Some are most potent fresh, and other can be dried or preserved in alcohol (tinctures), steeped as teas (infusions), simmered (decoctions), extracted by vinegar (acetractions), syrups, vegetable glycerin or honey. Freeze dried herbal powders are made into tablets, capsules, pastes or concentrates (4-6 times

* M.D. Clinical Professor, Mount Sinai School of Medicine, New York, NY.

regular strength). Herbs may also be given as suppositories, creams, liniments, oils (aromatherapy) or baths.

A belief held by many is that herbs are not drugs and are therefore safe. However the word “drug” is derived from an ancient word for “root” and thus, by definition, herbs are drugs. And, as many cases here proved, herbal use is not always safe and can even result in a fatal outcome. The touted association between “herbs”, “natural”, “Mother nature” and the implication of safe can be further compared. In nature, water is essential to survival, mud is important for planting and clay making. However, torrential rains and mudslides cause massive destruction and loss of life (Venezuela, December 1999). Clearly this is an example of an adverse natural interaction that is fatal.

Some of the recent resurgence in the interest in the United States in herbal medicine may be for several reasons:

- 1) Use of Western medicines may not always have good results.
- 2) Increase in travel and exposure to other cultures have revived and expanded many traditions. A certain exotic air is added to such therapies as ginseng, ma huang, etc.
- 3) High costs of medical care may force the public to seek what are perceived as less expensive therapies.
- 4) Advice to eat less fat meat has resulted in great consumption of leafy vegetables and leafy herbs (there is no clear demarcation between the two e.g. chicory, parsley, comfrey).
- 5) Herbs make vegetarian meals more palatable.
- 6) The American Heart Association has recommended decreasing salt intake. A herbal substitute might be basil, black pepper, garlic powder, mace, marjoram, onion powder, parsley, sage, savory, thyme (of each, 1 part) and added to cayenne pepper (1/2 part).
- 7) Recommendation to increase fiber intake. Herbs are generally high in fiber.
- 8) Use of vitamin A and C as antioxidants, both of which are common in many herbs.

- 9) Ready availability of many preparations over the counter.
- 10) In a safety conscious nation, wide advertising and use of the word “safe” is made in connection with herbs and nutritional substitutes.
- 11) Many herbs do exert beneficial effects.

It is estimated that approximately 20% of the adult population in the United States, take herbal medicines, megavitamins or both along with prescription drugs⁴. In this regard, annual expenditures on herbal therapies alone have exceeded of \$5 billion in recent years³. It is important to understand the pharmacodynamics and pharmacokinetics of these self-prescribed formulations, and to be able to provide adjunctive therapy for treatment of unexpected drug-induced responses perioperatively. Also, 42% of adult Americans have used at least one alternative therapy in recent years⁴.

Relaxation techniques and herbs have been advocated to treat chronic medical conditions such as diabetes, cancer, arthritis or AIDS⁵. It should however, be noted that the majority of these individuals did not receive advice from an alternative medicine practitioner with regard to treatment choice.

Insurance plans and managed care organizations are beginning to offer reimbursement for alternative treatments^{5,6}. Coverage of chiropractic treatment is mandated by law in least 45 States in the USA, acupuncture in 7 States and naturopathy in 2 States. Insurance plans that cover alternative health care often require physician referral for these services, highlighting the importance of physician awareness for less conventional therapies^{5,6}.

Also especially problematic for physicians is that many patients who take herbal preparations do not tell their doctors of this practice believing it to be “safe” and “natural” and thus not “drug” related. A recent study in Boston of 3842 patients indicated that 22% used herbal remedies and 51% took vitamins. Women and patients aged 40-60 were most likely to use herbals⁶. Use of complementary and alternative medicine increased from 34% in 1990 to 42% of all US adults by 1997. Yet another study of

2560 patients in California indicated that 39% used alternative medicines, 44% had not sought medical advice and 56% did not tell their anesthesiologist before surgery⁷. Higher educated Caucasian women were more likely to take herbal remedies.

Government Regulation

Several inconsistencies exist regarding manufacturing, promotion of health claims, potency and purity of compounding regarding herbal preparations. Herbal remedies are not held to the same standards and regulations as the FDA maintains for the pharmaceutical industry. Phased trials are not required though the FDA can “suggest” provision of scientific data to consumers. Herbs are not patented. However, recent regulation permits patenting of certain combinations of herbs.

Although the Dietary Supplement Health and Education Act of 1994 places the burden of product safety assurance on the manufacture, the FDA assumes the responsibility to prove that a product is unsafe. Thus, only if the FDA has reason to believe that an herb is unsafe, can it remove the drug from the market. Nevertheless, as noted above, the FDA is not and cannot test all herbal preparations before they are available over the counter.

Safety and health claim practices continued to be concerning and on April 29, 1998 the FDA put forth the “Regulations on Statements Made for Dietary Supplements Concerning the Effects of the Product on the Structure of Function of the Body”. These regulations state that “under the proposal dietary supplements that expressly or implicitly claim to diagnose, treat, prevent or cure a disease continue to be regarded as drugs and have to meet the safety and effectiveness standards for drugs under the Food, Drug and Cosmetic Act”. The definition of disease is “any deviation from, impairment of, or interruption of the normal structure of function of any part, organ or system... of the body that is manifested by a characteristic set of one or more signs or symptoms...” This definition allows the claim “promotes vascular health” while disallowing the statement “decreases blood pressure”. In response to the regulations,

herbal manufactures now add information that their product “is not intended to diagnose, treat, cure or prevent any disease” and thus is not subject to the FDA drug regulations. Further, the FGDA established a Special Nutritionals Adverse Monitoring System in 1993. By 1998, 2621 adverse reactions and 184 fatalities had been logged. Monitoring stopped in October 1998 and now only “Medical Emergencies” are collected.

Both the American Society of Anesthesiologists (ASA) and the New York State Society of Anesthesiologists (NYSSA) have addressed the seriousness of drug interactions with herbal preparation and anesthetics. The ASA has produced a pamphlet (Considerations for Anesthesiologists: What you should know about your patient’s use of Herbal Medicines: available from the ASA, 520 N. Northeast Highway, Park Ridge, IL 60068-2573, www.ASAhg.org, ©1999). The NYSSA issued a warning as a newsletter, (Herbal Medicines Can Have a Significant Impact During Surgery, Monitor Spring 1999; available from the NYSSA, 85 5th Ave., 8th Fl, New York, NY 10003 www.nyssa.pga.org).

History of Herbal Medicine

The history of herbal medicine is inextricably intertwined with that of modern medicine⁸. Many drugs listed as conventional medications were originally derived from plants. Some herbs are of historic importance. For example, white willow bark, and meadowsweet plant are the basis for salicylic acid, a precursor of aspirin; foxglove plant is the basis for digitalis, cinchona bark is the precursor to quinine compounds, periwinkle provides the chemotherapeutic agent, vincristine. The most widely used narcotic, morphine is derived from the opium poppy. Many additional potentially therapeutic agents, derived from herbs have been made available in recent years.

The Middle East has a rich history of utilization of herbal medicines. There are texts surviving from the ancient cultures of Greece, Egypt, India and Mesopotamia that describe and illustrate the use of many therapeutically useful plant products, including castor oil, linseed oil and white poppies. In the scriptural book of Ezekiel, which dates from the 6th

century B.C., an excerpt describes plant life, "... and the fruit thereof shall be for meat, and leaf there of for medicine". Egyptian hieroglyphs show physicians of the first and second centuries B.C., treating constipation with sienna pods, and using caraway and peppermint to relieve digestive dyscrasias. The medical papyri reveal substantial use of hyoscyamus, scopolamine, and opium poppy along with ritual and medical procedures. This extensive Egyptian pharmacopoeia later influenced the Greek, Roman, Hebrew and Arabic practice of medicine. The use of plants as medicine is older than recorded history. A mute witness to this fact, marshmallow root, hyacinth and yarrow have been carefully placed around the bones of a stone-age man in Iraq. Ancient Indian civilizations had developed a well-defined system of practice of herbal medicine called the *Ayurvedic* system of medical practice. The diseases were treated on the basis of text written in one of the vedas, known as *Ayurveda* (a book on practice of herbology). Ayurvedic system of practice of herbal medicine is still prevalent in the Indian subcontinent. The Chinese traditional system of medicine was developed by individual scholars as well as by government institutions in ancient times. Medical practice in China was primarily based on the work of the emperor Shen Nung (2800 B.C.), who was an authority on the medical use of herbs, and Huang Ti (2600 B.C.), who is generally credited as having originated the medical classic called *Nei Ching*. Shortly thereafter, the Chinese published the first book of materia medica. The latter was revised and expanded from time to time. The records of King Hammurabi of Babylon (c. 1800 B.C.) include instructions for using medicinal plants. Hammurabi prescribed the use of mint for digestive disorders.

Paulus Aegineta, the preeminent Greek physician, who probably lived about the 6th-7th century A.D., must be credited with giving us the greatest insight into ancient materia medica. In seven books he presented a complete view of the knowledge possessed by the Greeks, Romans and Arabians on all subjects connected with medicine and surgery. This opus was translated into English by Francis Adams in the 19th century (see the seven Books of Paulus Aeginata in 3 volumes. Trans F. Adams The Sydenhan Society London 1846). The 7th book contains an account of all medicines, simple and compound. The ancient authorities that Paulus

Aeginata drew upon included Hippocrates, Discorides (de Materia Medica) Celsus, Scribonius, Marcellus Empiricus, Pliny; Rei Rusticae, Scriptorum; Apuleius (de Herbis), Antonius Musa (de Herba Botanica), Macer, Floridus, Galenus, Aetius, Oribasius, Avicenna, Ebn Baithar, among many others. He credits Discorides as the first and greatest authority on the Materia Medica. Paulus listed 90 minerals, 700 plants and 168 animal substances for a total of 958 therapeutic preparations. The Arabs added camphor, sienna, musk, nux vomica and tamarinds among others to the Greek Materia Medica. By far, the most prolific in the Arab world appears to be Ebn Baithar who listed 1400 medical and dietary articles. In his commentary of this compilation by Paulus Aegineta, Francis Adams notes that it is quite clear that the Greek, Roman and Arabian physicians were amply provided with medicines of every possible character and he concludes that there is no reason to suppose that the latter were in anyway behind the physicians of the 19th century. Indeed the indications, effects and even drug interactions were well recognized and documented with few additions and changes over 1500 years.

Throughout the Middle Ages, homegrown botanicals were the only medicines readily available, and for centuries, most households possessed a carefully tended and extensively used herb garden. For the most part, herbal healing lore was passed from generation to generation by word of mouth. A father taught his son, the village herbal practitioner taught his most promising apprentice. By the 17th century, the knowledge of herbal medicine was widely disseminated throughout Europe and in 1649, Nicholas Culpeper wrote a physical directory and a few years later, produced *The English Physician*. This widely acclaimed herbal pharmacopoeia was one of the first generally available manuals that a layperson could use for health care. Culpeper studied at Cambridge University to become a physician. He chose to apprentice to an apothecary and eventually set up his own shop serving the poor people of London and became known as their “neighborhood doctor”.

Perhaps the most interesting addition to the world’s pharmacopoeia occurred towards the end of the 18th century with the discovery of the

diuretic effects of the foxglove. The herb had been incorporated with 20 or more other ingredients into a secret family recipe prescribed with some success by an old woman in Shropshire, England. Dr. William Withering, a physician at the General Hospital at Birmingham was asked about this cure in 1775. He realized that the active ingredient could only be digitalis and he started to use the herb in his practice, mainly for the sick poor at the hospital. As a result of his work, he published a review of the effects of the therapy in 163 cases. (*An Account of the Foxglove*, William Withering, Birmingham. Printed by M. Sweeney for GGJ and J. Robinson, Paternoster-Row, London, 1785). He describes both successes and failures and contributes poor outcome mainly to wrong indications for overdose. The book might also be described as a multi center study as he adds case reports from other practitioner's. One series, communicated from Dr. Jones, tabulates his results in 24 cases. There were 5 failures in cases of anasarca and asthma.

The first U.S. Pharmacopoeia was published in the year 1820. This volume included an authoritative listing of the herbal drugs, with description of their properties, uses, dosages and tests of purity. It was periodically revised and became the legal standard for medical compounds by the turn of the century.

A comprehensive textbook, (*Handbook of Medicinal Herbs* by James A. Duke. CRC Press, Boca Raton, Florida. 677pp) was published in 1985 and quickly went through many reprintings. The book treats 365 folk medicinal species, based on the rather folksy belief of the author that "a herb a day can help keep the doctor away (may be even cancer)" Although Dr. Duke admits that he did not coin the phrase "Herbal Renaissance", he notes that there are symptoms of such a rebirth and he cautions that we can expect more bad and good experiences as the use of herbs and compounds of herbs, doubles. He suggests that avoidance of the bad experiences with good herbs and survival of interesting experiences with bad herbs can come from public education and physician awareness. Today, the Physicians' Desk Reference, distributed to all doctors in the US, publishes a Guide to Natural Medicinal Therapies, which is updated annually.

Drugs from Herbs

Once scientific methods were developed to extract and synthesize the active ingredients from useful medicinal plants, pharmaceutical laboratories took over from the providers of medicinal herbs as producers of modern drugs⁹. 30% of all modern conventional medicines are derived from plants⁹. Some of the drugs, of importance in the perioperative period, derived from plants are listed below in Table 1.

Table 1

Plant	Drug
Atropa Belladonna	Atropine
Digitalis Purpurea	Digitalis
Papaver somniferum	Morphine
Cephaelis ipecaucuanha	Ipecac
Physostigma venenosum	Physostigmine
Ephedra sinica	Ephedrine
Erythroxyton coca	Cocaine
Datura fastuosa	Scopolamine

- Many drugs commonly used in the operating room are derived from herbs.

It seems that even though the medical community has made tremendous advances in the knowledge of the pathophysiology of various disease processes, individuals still resort to alternative modalities including nutraceuticals. This observation is based on the fact that, more than one in three Americans is currently using an herbal preparation⁴.

Commonly used Herbs

At present, there are approximately 20,000 herbal products available as over-the-counter therapeutic agents in the United States. A relatively recent survey of 163 health food retail stores in the United States revealed that the top 10 selling herbs were, Echinacea (*Echinacea purpurea*, *Echinacea pallida* and *angustifolia*), garlic, goldenseal (*Hydrastis*

canadenis), ginseng (*Asian Panax ginseng* and *American Panax quinquefolius*), ginkgo (*Ginkgo biloba*), saw palmetto (*Serenoa repens*), aloe (*Aloe species*), ma huang (*Ephedra sinica*), siberian ginseng (*Eleutherococcus senticosus*) and cranberry (*Vaccinium macrocarpon*)¹⁰. Current trends suggest St. John's Wort (*Hypericum perforatum*), valerian (*Valeriana officinalis*) and feverfew (*Tanacetum parthenium*) are likely soon to be listed among the top 10 herbal agents⁵.

Echinacea

The Echinacea are members of the daisy family and grow widely throughout North American plains, prairies, and woodlands. Although there are nine species of Echinacea altogether, medicinal preparations are primarily derived from three. These include Echinacea pallida (pale purple coneflower), Echinacea purpurea (purple coneflower) and Echinacea angustifolia (narrow leaved coneflower). Unlike over-the-counter decongestants or antihistamines, alkylamide and polysaccharide constituents of echinacea possess significant *in vitro* and *in vivo* immunostimulation properties due to enhanced phagocytosis and nonspecific T-cell stimulation¹¹. However the literature suggests that there is a paucity of scientific trials on echinacea and only a minority of these trials have been well designed. In a randomized, double-blind, placebo-controlled study involving 302 volunteers taking *E. angustifolia* and *E. purpurea* roots versus placebo, the two echinacea compounds had subjective beneficial effects with regard to upper respiratory infection (rates of infection were 36.7% in placebo group, 32% in *E. angustifolia* group and 29.3% in the *E. purpurea* group¹². Although there appeared to be a trend towards a reduction of upper respiratory tract infections, the observations failed to achieve statistical significance. Similar trials have been conducted with outcomes essentially in agreement with the above¹³. The herb has also been used to aid in wound healing.

The most common side effect of this herb, after oral administration, is an unpleasant taste sensation¹⁴. A prolonged use of echinacea (more than 8 weeks) can cause tachyphylaxis, albeit through an unknown

mechanism¹⁵. There is a possibility of anaphylaxis even with a single dose of the herb, as it may cross-react with other allergens, especially with members of the sunflower family (asteraceae)¹¹. This herb can be potentially hepatotoxic if used along with other hepatotoxic agents (e.g. anabolic steroids, amiodarone, methotrexate and ketoconazole)¹⁶. Flavonoids from *E. purpurea* are known to inhibit the hepatic cytochrome P-450 3A4 and sulfotransferase^{17,18}. Use of Echinacea is contraindicated in systemic and autoimmune disorders.

Drug Interactions

The immunostimulatory effects of echinacea may offset the immunosuppressive actions of corticosteroids and cyclosporine. Since the herb is known to cause inhibition of the hepatic microsomal enzymes, its concomitant use with drugs e.g. phenytoin, rifampin, barbiturates, which are metabolized by the hepatic microsomal enzymes, should be avoided as such a combination can precipitate toxicity of these drugs.

Garlic

Garlic (*Allium sativum*) has been used for medicinal purposes, for centuries. The most active ingredient of garlic is allicin (contains sulfur, and combined with breakdown products, gives garlic its characteristic smell). Crushing the garlic clove activates the enzyme allinase which converts allin to allicin. Several studies have targeted its vasodilator and hypocholesterolemic activity^{19,11}. Garlic derivatives are also frequently used for antiplatelet, antioxidant and fibrinolytic effects^{20,21}. A 1994 British met analysis combined the results of 16 clinical trials and demonstrated garlic to be effective in reducing total cholesterol by 12%. Serum triglyceride levels were also decreased whereas HDL levels were unchanged compared with results obtained after placebo administration²². Nevertheless, other researchers have found no improvement in serum lipid profiles of patients with hypercholesterolemia taking garlic^{23,24}. The evidence supporting the use of garlic for hypertension is less substantial, with a few clinical trials showing modest decreases in systolic and diastolic blood pressure with the

use of garlic supplements¹⁰. Decreased platelet aggregation has been noted in conjunction when the herb has been taken to treat hyperlipidemia²⁵. There is a reported case of spontaneous spinal/epidural hematoma in an 87 year-old male, with associated platelet dysfunction related to excessive garlic ingestion²⁶. In this regard, garlic-induced decreased platelet aggregation has also been described²⁷.

Drug Interactions

Garlic may augment the effects of warfarin, heparin, non-steroidal anti-inflammatory agents (NSAIDs), and aspirin and may result in an abnormal bleeding time that can at least theoretically lead to an increased risk of intraoperative or postoperative bleeding. Awareness of this action is especially important for patients in the chronic pain setting who not infrequently have tried many different types of therapy and now may present for a neuraxial block. The anesthesiologist should be aware of the potential for coagulopathy when spinal or epidural anesthesia is considered.

Ginger

Ginger (*Zingiber officinale*) has been described as an effective adjuvant against nausea, vomiting, motion sickness and vertigo. Anti-vertigo effects of ginger have been observed as compared to placebo with no study subjects experiencing nausea²⁸. In comparing the effect of diphenhydramine and ginger in the treatment of motion sickness, results demonstrated that ginger exerted a superior anti-motion sickness response. These studies further concluded that ginger exerts a gastric mechanism unlike diphenhydramine, which has a central nervous system mechanism²⁹. Ginger has been found to be effective in controlling the symptoms in hyperemesis gravidarum³⁰. A systematic review of 6 studies of the antiemetic effects of ginger identified 3 on postoperative nausea and vomiting³¹. Two of the studies found ginger to be superior to placebo and equal to metoclopramide. One study each for seasickness, morning sickness and chemotherapy induced nausea all favored ginger. Other trials

concluded that ginger was ineffective in reducing the incidence of postoperative nausea and vomiting in patients undergoing gynecologic laparoscopic surgery³². Ginger has been found to be a potent inhibitor of thromboxane synthetase enzyme, which can prolong bleeding time³³. The root may also be used as seasoning and as a taste enhancer with other less palatable herbs.

Drug Interactions

Use of ginger may increase bleeding time; therefore, its use should be avoided in patients on anticoagulants like warfarin and heparin or drugs such as NSAIDs and aspirin. The caveat about neuraxial blocks as noted above also applies.

Gingko biloba

Also known as Maidenhair-tree, the extracts from the leaves of the *Gingko biloba* tree have been used in traditional Chinese medicine for centuries¹⁰. The ginkgo tree is known to have an average life of approximately 1000 years. Its remarkable resilience allowed it to survive the atomic blast at Hiroshima. Asian civilizations have used this herb since 3000 BC to cure many ailments. It was brought to the United States around 1780's but it was not until the 1980's that the therapeutic value of ginkgo was studied⁴. The use of ginkgo biloba is on the rise in the United States. In 1997, it was one of the best selling herbs on the United States market, with sales in excess of \$240 million³⁴. The most important components are flavinoids, terpenoids, and organic acids. Metabolic pathways vary with different compounds¹⁰. Thus far, four preparations of ginkgo have been used in clinical trials, namely tebonin, tanakan, rokan and kaveri. The extract from the first three forms has been classified as EGB761.

The herb is used as an antioxidant, circulatory stimulant, and for the treatment of intermittent claudication, tinnitus, vertigo, memory enhancement, and sexual dysfunction⁴. A large placebo-controlled,

double-blind, randomized trial of EGB761 studied the effectiveness in patients with dementia and concluded that ginkgo extract was capable of stabilizing and modestly improving cognitive performance and social functioning ability³⁵. Further, ginkgo biloba has been shown to have potential for improvement of symptoms of intermittent claudication^{36,37}. Study subjects using ginkgo biloba experienced reduction in pain in their lower extremities with an improved claudication distance. The herb has the potential to inhibit platelet-activating factor, modulate nitric oxide, and possesses an anti-inflammatory effect³⁶⁻⁴¹. Ginkgo biloba is considered to be relatively safe with few side effects, limited to mild gastrointestinal upset and headache. However, a few disturbing case reports have been published. Ginkgo biloba-induced spontaneous hyphema (bleeding from the iris in the anterior chamber of the eye), subarachnoid hemorrhage, and spontaneous bilateral subdural hematomas have been described⁴²⁻⁴⁵. Of additional concern is the ginkgo toxin in both the ginkgo leaf and seed, which is thought to be neurotoxic⁴⁶.

Drug Interactions

Although there have been no placebo-controlled double-blind studies regarding potential ginkgo-induced abnormal bleeding, concomitant use with aspirin, or any NSAIDs and anticoagulants such as warfarin and heparin, is not recommended as ginkgo may increase the potential to bleed in these patients. It would also be reasonable to avoid its concomitant use with anticonvulsant drugs (e.g. carbamazepine, phenytoin, and phenobarbital) as it may decrease the effectiveness of these highly useful agents¹⁶. In addition, it has been suggested that ginkgo should be avoided in patients taking tricyclic antidepressant agents, as ginkgo might increase seizure threshold lowering efficacy¹⁶.

St. John's Wort

Known colloquially as St. John's Wort, *hypericum perforatum*, is approved in Germany for the treatment of anxiety, depression sleep related disorders and vitiligo among many other ailments. Hypericum has

also been used to dye wool and silk a deep violet red. In 1993, more than 2.7 million prescriptions for this herb were written in Germany, and in 1994, over 66 million daily doses were taken, making it the 7th most popular medicine in that country⁴⁷. Other names for this herb are *hardhay*, *amber*, *goatweed*, *klamath weed* & *tipton weed*. The Greek name, *Hypericum*, means “over an apparition” in the belief that the herb was so repellent to evil spirits that only a whiff would dispel them. Active compounds include, naphthadihydrodianthrones, particularly hypericin and pseudohypericin; flavinoids including quercitrin, rutin and hyperin⁴.

The mechanism of action of this herb is controversial. *Hypericum* extract inhibits isoforms of monoamine oxidase *in vitro*, but this has not been observed in *in-vivo* experiments⁴⁸. *In-vitro* studies have shown inhibition of GABA receptors by hypericum, which suggests a mode of action for the antidepressant effect of the herb^{49,50}. However, additional *in-vivo* studies are needed to more precisely confirm this observation. According to some researchers, serotonin receptor inhibition may be the underlying mechanism responsible for the antidepressant action⁵¹. Although with considerable statistical flaws, a meta-analysis showed St. John’s Wort to be more promising in the treatment of mild to moderate depression as compared to placebo but further studies with standardized variables are needed⁵².

Side effects described include dry mouth, dizziness, fatigue, constipation and nausea. The most prominent adverse effect, attributed to its hypericin component, is photosensitivity⁵³. There have been no reports of any adverse effects on cardiac conduction although if used concomitantly with a selective serotonin reuptake inhibitor (SSRI) e.g. fluoxetine or paroxetine, it can cause a serotonergic syndrome, which is characterized by tremors, hypertonicity, myoclonus, autonomic dysfunction, hallucinosis, hyperthermia and even death^{10,54}.

Drug Interactions

Concomitant use of St. John’s Wort is currently not recommended with photosensitization drugs (e.g. piroxicam and tetracycline

hydrochloride), monoamine oxidase inhibitors (e.g. phenelzine), β -sympathomimetic amines (e.g. ma huang, pseudoephedrine hydrochloride or SSRIs (e.g. fluoxetine or paroxetine).

Ginseng

There is a wide variation in the components of this herb. Depending upon its origin, ginseng can be classified as *American ginseng* (*Panax quinquefolius* grows in the United States), *Chinese ginseng*, or *Korean ginseng* (*Panax ginseng*) or *Sanchi/Tienchi* (*Panax notoginseng*). American and Oriental ginseng are nutritionally similar. It should however be noted that *Siberian ginseng*, also known as *Eleutherococcus senticosus*, belongs to a different genus⁴. The active compound in panax ginseng is ginsenoside. In ancient times, the herb was used as an aphrodisiac, anti-aging and energy-boosting tonic. It is also used by modern day athletes, to increase their “energy levels” and is used as an antioxidant⁵⁵⁻⁵⁷. The herb is extremely popular and has been labeled as an adaptogenic, augmenting adrenal steroidogenesis via a centrally mediated mechanism⁵⁸. Ginseng’s immunomodulatory effects have been described and studies have shown an ginseng-induced hypoglycemic effect^{59,60}. This hypoglycemic effect have been attributed to ginsenoside Rb2 and panaxans I, J, K and L⁶¹⁻⁶⁵.

Adverse effects described include hypertension, insomnia, headache, vomiting, and epistaxis^{66,67}. Stevens-Johnson syndrome, postmenopausal vaginal bleeding, mastalgia and diffuse breast nodularity have been associated with the use of this herb⁶⁸⁻⁷¹. Ginseng should be avoided in pregnancy, in children, lactating women, and in patients with cardiovascular disease^{4,16}. One fatality associated with ginseng laced with ma huang has been described⁷². Ginseng has been reported at least in one case to interact with warfarin with clinically relevant coagulation modulation⁷³. In this regard a study postulated that there may be some antiplatelet components in ginseng⁷⁴.

Drug Interactions

The use of ginseng should be avoided in patients on drugs like warfarin, heparin, NSAIDs and aspirin. Since ginseng can cause hypertension, attention should focus on perioperative hemodynamic variation as these patients are often volume depleted and since many anesthetic agents can cause generalized vasodilator effects intraoperative hypotension may result. Concomitant use of ginseng with monoamine oxidase inhibitors (e.g. phenelzine sulphate), should be avoided as manic episodes have been reported with routine use of ginseng^{75,76}. Ginseng, with its potential hypoglycemic effects, should be avoided or at least be cautiously used in patients on insulin or oral hypoglycemic medications. Also, blood glucose levels should be monitored perioperatively in patients at risk. (e.g. neurosurgical patients receiving steroids, patients with diabetic end stage renal disease).

Piper methysticum (Kava kava)

Kava-kava is commonly used for its anxiolytic properties. For centuries, this herb has been used by Pacific islanders, as a part of their ceremonial rituals where it is used as fermented liquor made from the upper portion of the rhizome⁴. Kava lactones are the active compounds contained in the herb. The herb is found in Polynesia, Melanesia and Micronesia⁷⁷. It has been used in Germany to treat gonorrhoea and the Hawaiians used it for treating certain skin diseases⁷⁸. It is said to relax the mind and body, ease pain and induce a restful sleep which is not followed by a hangover. The herb has been attributed with anesthetic, analgesic, anti-convulsive, anti-fungal, sleep inducing and spasmolytic properties. Kava-kava can cause visual alterations, ichthyosiform dermatopathy, and hallucinations^{4,5,79}. With regard to analgesic mechanisms, antinociceptive effects produced by Kava-kava may be similar to local anesthetic responses^{80,81}. The inhibition of noradrenaline may contribute to the psychotropic qualities of the herb⁸².

Drug Interactions

Ethanol can increase the hypnotic effect of Kava-kava and it should be avoided in patients with endogenous depression as it increases the risk of suicide^{83,84}. Kava-kava can potentiate the effects of barbiturates and benzodiazepines and can cause excessive sedation⁸⁵.

Chrysanthemum (Tanacetum) Parthenium (Feverfew)

Introduced to the Americas as an ornamental medical herb, it is used as an insecticide in Mexico and was also advocated as an alternative for aspirin. The most common use now is for migraine headaches. Other names for this herb are featherfew, featherfoil, midsummer daisy, bachelor's button, wild chamomile and compositae⁴. Parthenolide is the active compound. The word feverfew is derived from the Latin word, febrifugia, meaning, "fever reducer". A double-blind placebo-controlled trial found a 70% reduction in migraine frequency in patients taking feverfew⁸⁶. In a randomized controlled trial using a different preparation of feverfew, migraine headaches were not preempted⁸⁷. There is considerable lack of standardization in the quantity of the active ingredient, parthenolide, in most of the feverfew preparations which further increases the difficulty to conduct precise clinical trials on this herb⁸⁸. Feverfew inhibits serotonin release from aggregating platelets possibly related to inhibition of the release of arachidonic acid via a phospholipase-linked mechanism⁸⁸⁻⁹⁰. The herb has been found to reduce prostaglandin production by 86% to 88% without inhibiting the cyclooxygenase enzyme⁹¹.

Adverse effects include aphthous ulcers and gastrointestinal irritability. Rebound headache may be associated with cessation of the use of the herb. Feverfew is not recommended for children, pregnant patients or nursing mothers⁹². Post feverfew syndrome is characterized by nervousness, headaches, insomnia, arthralgias, joint stiffness and fatigue⁹³.

Drug Interactions

Feverfew can inhibit platelet activity and it is suggested to avoid the use of this herb in patients taking medications such as, heparin, warfarin, NSAIDs, aspirin and vitamin E^{94,95}. Tannin-containing herbs like feverfew can interact with iron preparations, thereby reducing their bioavailability¹⁶.

Ephedra sinica (Ma huang)

This herb was listed in Shen Neng's classic text on medicinals as one of 365 herbs, as early as the 1st century AD⁹⁶. The herb is traditionally used for treatment of the common cold, flu, various allergic symptoms, bronchitis, low blood pressure, fever, asthma, arthritis and fluid retention. Native-Americans have used ephedra as an external application for sore healing⁴.

It acts as a sympathomimetic agent, and possesses positive inotropic and chronotropic responses. Ephedra also has bacteriostatic and antitussive actions. It is a cardiovascular stimulant (acts as an α or β -adrenergic agonist) and is a potent bronchodilator⁹⁷. Because it increases metabolic rate, ephedra is contained in many over-the-counter weight reduction preparations. Indeed it is component of over 5.000 products.

Adverse effects of this herb include hypertension, tachycardia, cardiomyopathy, cardiac dysrhythmias, myocardial infarction, cardiovascular accidents, seizures, psychosis and/or death. Over 200 fatalities have been linked to its use and interactions and these deaths have been attributed to a lack of standardization in the formulation^{98,99}. The Bureau of Food and Drug Safety of the Texas Department of Health has reported 8 deaths associated with ephedrine-containing compounds during a 21-month period between 1993 and 1995. Seven of these deaths were secondary to myocardial infarction or cerebrovascular accident⁴. Sales of the herb are now banned in New York.

Drug Interactions

Ephedra can interact with volatile general anesthetic agents (e.g. halothane) and cardiac glycosides (e.g. digitalis) to cause cardiac dysrhythmias. Patients on ephedra, under general anesthesia, can have severe hypotension that must be controlled with 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 can cause hypertension¹⁰⁰.

Other Commonly used herbs

Several herbs are used that may or may not have perioperative implications.

Goldenseal is used as a mild laxative and to reduce inflammation. It may increase hypertension. It is widely used for intestinal problems, and may increase blood pressure or cause electrolyte imbalance from diarrhea. *Saw Palmetto*, given for urinary difficulties may interact with other hormone therapies. *Valerian*, used for its sedative and muscle relaxant effects, may increase the effectiveness of antiseizure medications and prolong action of other sedatives. Although not an herb, *colloidal silver* has been advocated as a cure all. Advertisements claim that the preparation may be inhaled or ingested in large quantities on a daily basis. Undoubtedly there is little actual silver in the liquid prescribed; long term use has been associated with development of a gray hue to the skin. Also, nasal inhalation may cause long term pulmonary problems.

Anesthesia and Herbal Medicine

There are several case reports relating to herbal medicine/anesthesia interactions, underscoring the complex nature of the interactions and substantiating the need for well-designed scientific studies to elaborate the anesthetic responses in patients taking over-the-counter herbs. In one report, a 42-year-old obese male patient had a cardiac arrest, 20 minutes

after receiving epidural anesthesia¹⁰¹. The patient was stabilized after cardiopulmonary resuscitation, and blood samples were taken which later revealed low plasma renin and aldosterone levels. It was determined that the patient was taking an herbal medicine containing ethoxybenzamide, which is a NSAID, for one and a half years. The cardiac arrest was believed to be related to NSAID-induced hyporeninemic hypoaldosteronism, superimposed on epidural anesthesia-induced sympathectomy.

Rarer agents have also been studied. A traditional Chinese herbal medicine, Huatuo reconstructive pill (HRTP) used for thousands of years with a described “remarkably beneficial effect” on cerebral palsy, has been studied in anesthetized animals¹⁰². Carotid blood flow was selectively increased without changing vascular resistance of the hind limb. The internal carotid blood flow reached as high as 173% of the control level. A positive inotropic action was demonstrated by an increase in left ventricular pressure and cardiac output without changes in heart rate, blood pressure, electroencephalogram, electrocardiogram, or respiration.

Physicians, irrespective of their specialty, should not underestimate the potential risks associated with the use of herbs as reports document within the last two decades more than 100 direct herbogenic deaths¹⁰³; many serious complications have been reported; patients have required renal dialysis, renal transplantation and hepatic transplantation after taking botanicals¹⁰⁴⁻¹¹⁰.

Case Illustration

A 66-year-old obese Caucasian female, was scheduled for left total knee replacement. During her pre-operative evaluation, she told the internist that she had been taking herbal formulations, containing Kava-kava, ginkgo biloba, and St. John's Wort to cure her depression. She had been consuming these capsules regularly for the last eighteen months. She had not told her surgeon because she felt that the herbs were mere supplements and not “actual” medicine. A review of systems revealed a

questionable history of recent gingival bleeding. Her cardiovascular and respiratory systems were unremarkable. Preoperative laboratory evaluation demonstrated a hemoglobin level of 9.2 gm/dl. Chest radiograph and electrocardiogram were within normal limits. A bleeding time was found to be abnormal at 16 minutes. Both PT and PTT were elevated.

After discussion with the surgeon, the procedure was rescheduled, and the patient referred for psychiatric evaluation. This decision was based on the potential risk of abnormal bleeding and herb-drug interaction during anesthesia. Kava-kava can potentiate the effects of barbiturates and benzodiazepines and is contraindicated in patients with endogenous depression as it is thought to increase the risk of suicide. St. John's Wort may have mild monoamine oxidase inhibitory effects or act as a selective serotonin reuptake inhibitor (SSRI). Until the monoamine oxidase inhibitory status of St. John's Wort has been defined, it would be prudent to avoid its concomitant use with known monoamine oxidase inhibitors such as phenelzine or β -sympathomimetic amines like pseudoephedrine. As described above, ginkgo biloba-induced responses carry a potential risk of excessive bleeding.

A list of other potential herb-drug interactions is presented in Table 2.

Table 2
Herbal Medications and Anesthesia

- | |
|---|
| <ul style="list-style-type: none"> ■ Echinacea offsets immunosuppression, inhibits HME* ■ Garlic augments heparin, NSAIDs ■ Ginger increases bleeding time ■ St. John's Wort reacts with MAO inhibitors, tetracycline ■ Kava-kava reacts with ethanol, excessive sedation ■ Feverfew inhibits platelet activity ■ Ephedra interacts with inhalation anesthetics ■ Ginseng causes hypertension, hypoglycemia, reacts with MAO inhibitors |
|---|

* HME = hepatic microsomal enzymes.

Summary

Needs Assessment

Herbal medicines have enormous presence world wide. Herbs are listed under the “supplement” category by the food and Drug Administration in the USA. The Dietary Supplement and Health Education Act signed into law in October 1994, requires no proof of efficacy, no demonstration of safety, and sets no standards for quality control for the products labeled as “supplements” thereby increasing the risk of adverse effects as quantities of active agents are unregulated. The United States has experienced an epidemic of over-the-counter “natural” products over the last two decades; but there is little motivation for the manufacturers to conduct randomized, placebo-controlled, double-blinded clinical trials to unequivocally prove the safety and efficacy of these drugs. Physicians must enquire and be aware of herbal/drug interactions. In addition, patient education of the potential interactions should be a routine component of preoperative assessment. The American Society of Anesthesiologists (ASA) recommends that all herbal medications should be discontinued 2-3 weeks prior to an elective surgical procedure. If the patient is not sure of the contents of the herbal medicine, he/she should be urged to bring the container so that an attempt can be made to review the contents of the preparation. While such an action holds some promise in the elective setting, emergency care should be based on a thorough drug-intake history from the patient or a relative, if possible.

Medical research and medical literature in general has not addressed this new group of health supplements, despite the fact that many of these herbs have the potential to cause serious health problems and drug interactions. There is a need to conduct scientific clinical trials to study the anesthetic drug responses to commonly used nutraceutical agents.

References

1. HERBAL ROULETTE: *Consumer Reports*. 698-705, Nov. 1995.
2. EISENBERG DM, KESSLER RC: Unconventional medicine in the United States: prevalence, costs and patterns of use. *NEJ Med*; 328:246-252, 1993.
3. EISENBERG DM, DAVIS RB, ETTNER SL, ET AL: Trends in alternative medicine use in the United States, 1990-1997. *JAMA*; 280:1569-1575, 1998.
4. LEAK JA: Herbal Medicine: Is it an alternative or an unknown? A brief review of popular herbals used by patients in a pain and symptom management practice setting. *Cur. Rev. Pain*; 3:226-236, 1999.
5. WINSLOW LC, KROLL DJ: Herbs as medicines. *Arch. Intern. Med*; 158:2192-2199, Nov. 1998.
6. TSEN LC, SEGAL S, POTHIER M, ET AL: Alternative Medicine Use in Presurgical Patients. *Anesthesiology*; 93:148-51, 2000.
7. LEUNG JM, DZANKIC S, MANKU K, ET AL: The prevalence and predictors of the use of alternative medicine in presurgical patients in 5 California hospitals. *Anes and analg*; 93:1062-8, 2001.
8. www.cyberchat.uml.edu/fall98/31.302/student8/herbs3.htm History of Herbal medicine.
9. KLEINER SM: The true nature of herbs. *Phys Sports Med*; 23:13-14, 1995.
10. NESS J, SHERMAN FT, PAN CX: Alternative medicine: What the data say about common herbal therapies. *Geriatrics*; 54 (Oct): 33-43, 1999.
11. BAUER R, KHAN IA: Structure and stereochemistry of new sesquiterpene esters from *E. purpurea*. *Helv Chim Acta*; 68:2355-2358, 1985.
12. MELCHART D, WALTHER E, LINDE K, ET AL: Echinacea root extracts for the prevention of upper respiratory tract infections: a double-blind, placebo-controlled, randomized trial. *Arch Fam Med*; 7(6):541-545, 1998.
13. GRIMM W, MULLER HH: A randomized controlled trial of the effect of fluid extract of Echinacea purpurea on the incidence and severity of colds and respiratory infections. *Am J Med*; 106(2):138-143, 1999.
14. PARNHAM MJ: Benefit-risk assessment of the squeezed sap of the purple coneflower (*E. purpurea*) for long term oral immunostimulation. *Phytomedicine*; 3:95-102, 1996.
15. BLUMENTHAL M, GOLDBERG A, GRUENWALD J, ET AL: eds. German Commission E Monographs: Therapeutic Monographs on Medicinal plants for Human Use Austin, TX: American Bot. Council; 1998.
16. MILLER LG: Herbal Medicinals. *Arch. Intern. Med*; 158:2200-2211, Nov. 1998.
17. EATON EA, WALLE UK, LEWIS AJ, ET AL: Flavinoids, potent inhibitors of the human form of phenolsulfotransferase: potential role in drug metabolism and chemoprevention. *Drug Met Disp*; 24:232-237, 1996.
18. SCHUBERT W, ERIKSSON U, EDGAR B, ET AL: Flavinoids in grapefruit juice inhibit the invitro hepatic metabolism of 17 beta-estradiol. *Eur J Drug Met; Pharmacol*. 20:219-224, 1995.
19. REUTER HD: Allium sativum and Allium ursinum, part 2: pharmacology and medicinal applications. *Phytomedicine*; 2:73-91, 1995.
20. BEAGLEHOLE R: Garlic for flavor, not cardioprotection. *Lancet*; 348:1186-1187, 1996.
21. JAIN AK, VARGAS R, GOTZKOWSKY S, ET AL: Can garlic reduce levels of serum lipids? A controlled clinical study. *Am J Med*; 94(6):632-635, 1993.
22. SILAGY CA, NEIL HAW: A meta-analysis of the effect of garlic on blood pressure. *J Hypertension*; 12:463-468, 1994.
23. NEIL HAW, SILAGY CA, LANCASTER T, ET AL: Garlic powder in the treatment of moderate hyperlipidemia: a controlled trial and meta-analysis. *J R Coll Physician*; 30:329-334, 1996.

24. BERTHOLD HK, SUDHOP T, VON BERGMANN K: Effect of a garlic oil preparation on serum lipoproteins and cholesterol metabolism: A randomized controlled trial. *JAMA*; 279(23):1900-1902, 1998.
25. Cooperative group for essential oil of garlic: The effect of essential oil of garlic on hyperlipidemia and platelet aggregation: an analysis of 308 cases. *J Traditional Chin Med*; 6:117-120, 1986.
26. ROSE KD, CROISSANT PD, PARLIAMENT CF, ET AL: Spontaneous spinal epidural hematoma with associated platelet dysfunction from excessive garlic consumption: a case report. *Neurosurgery*; 26:80-88, 1990.
27. BORDIA A: Effect of garlic on human platelet aggregation *in vitro*. *Atherosclerosis*; 30:355-360, 1978.
28. GRONTVED A, HENTZER E: Vertigo-reducing effect of ginger root. *J Otolaryngol*; 48:282-286, 1986.
29. HOLTSMANN S, CLARKE AH, SCHERER H, ET AL: The anti-motion sickness mechanism of ginger. *Acta Otolaryngol*; (Stockh), 108:168-174, 1989.
30. FISCHER-RASMUSSEN W, KJAER SK, DAHL C, ET AL: Ginger treatment of hyperemesis gravidarum. *Eur J Obstet Gyn Rep Biol*; 38:19-24, 1990.
31. ERNST E, PITTLER MH: Efficacy of ginger for nausea and vomiting: a systematic review of randomized clinical trials. *Br J Anaesth*; 84:367-71, 2000.
32. VISALYAPUTRA S, PETCHPAISIT N, SOMCHAROEN K, ET AL: The efficacy of ginger root in the prevention of postoperative nausea and vomiting after out patient gynecological laparoscopy. *Anesthesia*; 53(5):506-510, 1998.
33. BACKON J. GINGER: Inhibition of thromboxane synthetase and stimulation of prostacyclin: relevance for medicine and psychiatry. *Med Hypoth*; 20:271-278, 1986.
34. GILLIS CN: Medicinal Plants Rediscovered. Semin Anesth. Periop. *Med Pain*; 17(4):319-330, 1998.
35. LEBARS PL, KATZ MM, BERMAN N, ET AL: A placebo controlled, double-blind, randomized trial of an extract of *Ginkgo biloba* for dementia. *JAMA*; 278:1327-1332, 1997.
36. BAUER U: 6-month double-blind randomized clinical trial of *gingko biloba* extract versus placebo in two parallel groups in patients suffering from peripheral arterial insufficiency. *Arzneimittelforschung*; 34(6):716-720, 1984.
37. PETERS H, KIESER M, HOLSCHER U: Demonstration of the efficacy of *Ginkgo biloba* special extract EGB 761 on intermittent claudication – a placebo controlled, double-blind multicenter trial. *Vasa*; 27(2):106-110, 1998.
38. BRAQUET P: BN 52021 and related compounds: a new series of highly specific PAF-acether receptor antagonists isolated from *gingko biloba*. *Blood Vessels*; 16:559-572, 1985.
39. BRAQUET P, BOURGAIN RH: Anti-anaphylactic properties of BN 52021: a potent platelet activating factor antagonist. *Adv Exp Med Biol*; 215:215-233, 1987.
40. MARCOCCI L: The nitric oxide scavenging properties of *gingko biloba* extract Egb761: inhibitory effect on nitric oxide production in the macrophage cell line RAW 264.7. *Biochem Pharmacol*; 53:897-903, 1997.
41. KOBUCHI H, LDROY-LEFAIX MT, CHRISTEN Y, ET AL: *Ginkgo biloba* extract (Egb 761): inhibitory effect on nitric oxide production in macrophage cell line RAW 264.7. *Biochem Pharmacol*; 53:897-903, 1997.
42. ROSENBLATT M, MINDEL J: Spontaneous hyphema associated with ingestion of *Ginkgo biloba* extract [letter]. *NEJM*; 336:1108, 1997.
43. ROWN J, LEWIS SL: Spontaneous bilateral subdural hematomas associated with chronic *Ginkgo biloba* ingestion have also occurred. *Neurol*; 46:1775-1776, 1996.

44. GILBERT GJ: Gingko biloba [commentary]. *Neurology*; 48:1137, 1997.
45. VALE S: Subarachnoid hemorrhage associated with Gingko biloba [letter]. *Lancet*; 352:36, 1998.
46. ARENZ A, KLEIN M, FIEHE K, ET AL: Occurrence of neurotoxic 4'-o-methylpyridoxin in gingko biloba leaves, Gingko medications and Japanese Gingko food. *Planta Med*; 62:548-551, 1996.
47. LOHSE MJ, MULLER-OERLINGHAUSEN B: Psychopharmaka. In: Schwabe U, Pffrath D, eds. *Arzneiverordnungsbuch '94*. Stuttgart, Germany: Gustav Fischer; 354-370, 1994.
48. STAFFELDT B, KERB R, BROCKMOLLER J, ET AL: Pharmacokinetics of hypericin and pseudohypericin after local intake of the Hypericum perforatum extract LI160 in healthy volunteers. *J Geriatr Psych Neurol*; 7 (Suppl I): S47-S53, 1994.
49. COTT JM: In vitro receptor binding and enzyme inhibition by Hypericum perforatum extract. *Pharmacopsych*; 30:108-112, 1997.
50. COTT JM, MISRA R: Medicinal plants: a potential source of new psychotherapeutic drugs. In new drug development from herbal medicines in *Neuropharmacology*, vol. 5. Edited by Kanba S, Richelson SE. New York, NY: Brunner/Mazel; 1998.
51. MULLER W: Effect of Hypericum extract on the suppression of serotonin receptors. *J Geriatr Psych Neurol*; 7:S63-64, 1994.
52. LINDE K, RAMIREZ CD, MULROW CD, ET AL: St. John's wort for depression-an overview and meta-analysis of randomized clinical trials. *BMJ*; 313:253-258, 1996.
53. MCGUFFIN M, HOBBS C, ET AL: *Botanical safety Hand-book*. American Herbal Products Association. Boca Raton, FL: CRC Press, 1997.
54. CZEKALLA J, GASTPAR M, HUBNER WD, ET AL: The effect of hypericum extract on cardiac conduction as seen in the electrocardiogram compared to that of imipramine. *Pharmacopsychiatry*; 30 (suppl 2): 86-88.
55. BAHRKE MS, MORGAN WP: Evaluation of ergogenic properties of ginseng. *Sports Med*; 18:229-248, 1994.
56. SHAN Y, XU XH, JIANG UP: Effects of ginsenosides on myocardial ischemia/reperfusion damage in open heart surgery patients. *Chung Hua I Hsueh Tsa Chih (Med J China)*; 74:626-628, 1994.
57. RIMAR S, LEE-MENGEL M, GILLIS CN: Pulmonary protective and vasodilator effects of a standardized panax ginseng preparation following artificial gastric digestion. *Pulm Pharmacol*; 9:205-209, 1996.
58. NG TB, LI WW, YEUNG HW: Effects of ginsenosides, lectins and Momordica charantia insulin like peptide on corticosterone production by isolated rat adrenal cells. *J Ethnopharm*; 21:21-29, 1987.
59. JIE YH, CAMMISULI S, ET AL: Immunomodulatory effects of panax ginseng: CA Meyer in the mouse. *Agents Actions Suppl*; 15:386-391, 1984.
60. SOTANIEUMI EA, HAAPAKKOSKI E, RAUTIO A: Ginseng therapy in non-insulin dependent diabetic patients. *Diabetes care*; 18:1373-1375, 1995.
61. YOKOZAWA T, KOBAYASHI T, OURA H, ET AL: Studies on the mechanism of hypoglycemic activity of ginsenoside-Rb2 in streptozotocin-diabetic rats. *Chem Pharm Bull*; 33:869-872, 1985.
62. OSHIMA Y, KONNO C, HIKONO H: Isolation and hypoglycemic activity of panaxans I, J, K and L, glycans of panax ginseng roots. *J Ethnopharm*; 14:255-259, 1985.
63. KONNO C, MURAKAMI M, OSHIMA Y, ET AL: Isolation and hypoglycemic activity of panaxans Q, R, S, R and U: glycans of panax ginseng roots. *J Ethnopharm*; 14:69-74, 1985.
64. KONNO C, SUGIYAMA K, KONNO M, ET AL: Isolation and hypoglycemic activity of panaxans A, B, C, D and E glycans of panax ginseng roots. *Planta Med*; 50:436-438, 1984.
65. TOKMODA M, SHIMADA K, KONNO C, ET AL: Partial structure of panax A: a hypoglycemic glycan of panax ginseng roots. *Planta Med*; 50:436-438, 1984.

66. BALDWIN CA: What pharmacists should know about ginseng. *Pharm J*; 237:583-586, 1986.
67. HAMMOND TG, WHITWORTH JA: Adverse reactions to ginseng [letter]. *Med J Aust*; 1:492, 1981.
68. DEGA H, LAPORTE J, FRANCES C. ET AL: Ginseng a cause of Steven-Johnson Syndrome [letter] *Lancet*; 347:1344, 1996.
69. GREENSPAN EM: Ginseng and vaginal bleeding [letter]. *JAMA*; 249:2018, 1983.
70. HOPKINS MP, ANDROFF L, BENNINGHOFF AS, ET AL: Ginseng face cream and unexpected vaginal bleeding. *Am J Obs Gyn*; 159:1121-1122, 1988.
71. PALMER BV, MONTGOMERY AC, MONTERRIO JCMP, ET AL: Ginseng and mastalgia. *BMJ*; 1:1284, 1978.
72. O'HARA MA, KEIFER D, FARRELL K, KEMPER K: A review of 12 commonly used medicinal herbs. *Arch Fam Med*; 7(6):523-536, Nov-Dec 1998.
73. JANETZKY K, MORREALE AP: Probable interactions between warfarin and ginseng. *Am J Health Syst Pharm*; 54:692-693, 1997.
74. KUO SC, TENG CM, LEE JG, ET AL: Antiplatelet components in panax ginseng. *Planta Med*; 56:164-167, 1990.
75. SHADER RI, GREENBLATT DJ: Phenelzine and the dream machine-ramblings and reflections [editorial] *J Clin Psychopharmacol*; 5:65, 1985.
76. JONES BD, RUNIKIS AM: Interactions of ginseng with phenelzine. *J Clin Psychopharm*; 7:201-202, 1987.
77. NORTON SA: Herbal medicines in Hawaii from tradition to convention. *Hawaii Med J*; 57(1):382-386, 1998.
78. NORTON SA, RUZE P: Kava dermatopathy. *J Am Acad Derm*, 31(1):89-97, 1994.
79. GARNER LF, KLINGER JD: Some visual effects caused by the beverage kava. *J Ethnopharm*; 13(3):307-311, 1985.
80. JAMIESON DD, DUFFIELD PH: The antinociceptive actions of kava components in mice. *Clin Exp Pharm Physiol*; 17(7):495-507, 1990.
81. SINGH YN: Effects of kava on neuromuscular transmission and muscular contractility. *J Ethnopharm*; 7(3):267-276, 1983.
82. SEITZ U, SCHULE A, GLEITZ J: [3H]-monoamine uptake inhibition properties of kava pyrones. *Planta Med*; 63(6):548-549, 1997.
83. JAMIESON DD, DUFFIELD PH: Positive interaction of ethanol and kava resin in mice. *Clin Exp Pharm Physiol*; 17(7):509-514.
84. GRUENWALD J, BRENDLER T, JAENICKE C, ET AL: *PDR for herbal medicines*, edn 1. Montvale, New Jersey: Medical Economics Compan; 1043-1045, 1998.
85. Piper methysticum (Kava Kava): *Altern. Med Rev*; 3(6):458-460, 1998 (needs author).
86. MURPHY J, HEPTINSTALL S, DOHERTY M, ET AL: Randomized double-blind, placebo-controlled trial of feverfew in migraine prevention. *Lancet*; 2:189-192, 1988.
87. DE WEERDT C, BOOTSMA H, HENDRICKS H: Herbal medicines in migraine prevention: randomized double-blind, placebo-controlled crossover trial of a feverfew preparation. *Phyomed*; 3:225-230, 1996.
88. MARLES RJ, KAMINSKI J, AMASON JT, ET AL: A bioassay of inhibition of serotonin release from bovine platelets. *J Nat Prod*; 55(8):1044-1056, 1992.
89. FOZARD JR: 5-Hydroxytryptamine in the pathophysiology of migraine. In *Vascular Neuroeffector Mechanisms*. Ed Bevan JA, Amsterdam, The Netherlands: Elsevier; 321-328, 1985.
90. MAKHEJA AN, BAILEY JM: A platelet phospholipase inhibitor from the medicinal herb feverfew (*Tanacetum parthenium*). *Prostaglandins Leukot Med*; 8:653-660, 1982.
91. COLIER JOH, BUTT NM, McDONALD-GIBSON WJ, ET AL: Extract of feverfew inhibits

- prostaglandins biosynthesis. *Lancet*, 2:922-923, 1980.
92. Drug information, U.S. Pharmacopoeia: US Pharmacopoeia Consumer Information. Feverfew. Rockville, MD: The United States Pharmacopoeial Convention, Inc; 1998.
93. BALDWIN CA, ANDERSON LA, PHILLIPSON JD, ET AL: What pharmacists should know about feverfew. *J Pharm Pharmacol*; 239:237-238, 1987.
94. HEPTINSTALL S, GROENWEGEN WA, SPANGENBERG P, ET AL: Extracts of feverfew may inhibit platelet behavior neutralization of sulphhydryl groups. *J Pharm Pharmacol*; 39:459-465, 1987.
95. MAKHEJA AN, BAILEY J: The active principle in feverfew [letter]. *Lancet*; 2:1054, 1981.
96. FOSTER S: Herbs for your health. LOVELAND CO: *Interweave Press*; 37-38, 1996.
97. TINKLEMAN DG, AVNER SE: Ephedrine therapy in asthmatic children. Clinical tolerance and absence of side effects. *JAMA*; 237(6):553-557, 1977.
98. GURLEY BJ, GARDNER SF, WHITE LM, ET AL: Ephedrine pharmacokinetics after ingestion of nutritional supplements containing ephedra sinica (ma huang). *Ther Drug Monit*; 20(4):439-445, 1998.
99. MMWR Morb Mortal Wkly Rep Aug 16, 45(32):689-693, 1996.
100. GRUENWALD J, BRENDLER T, JAENICKE C: *PDR for Herbal Medicines*; edn 1. Montvale, New Jersey: Medical Economics Co. 826-827, 1998.
101. PING-HENG T, AN-KUO C, JYH-SHYAN P: Accidental shock during epidural anesthesia in a patient with NSAID-induced hyporeninemic hypoaldosteronism. *J Clin Anesth*; 9:424-427, 1997.
102. JIAN HS: Hemodynamic actions of Huatuo reconstruction pill on anesthetized animals. *Adv Exp Med Biol* (United States), 363:183-187, 1995.
103. ELLENHORN MJ, SCHONWALD S, ORDOG G, ET AL: *Medical Toxicology: Diagnosis and treatment of human poisoning*. 2nd ed. Baltimore, MD: Williams & Wilkins; 1997.
104. VANHERWEGHAM JL, DEPIERREUX M, TIELEMANS C, ET AL: Rapidly progressive interstitial renal fibrosis in young women: association with slimming regimen including Chinese herbs. *Lancet*; 341:387-391, 1993.
105. ABT AB, OH JY, HUNTINGTON RA, ET AL: Chinese herbal medicine induced acute renal failure. *Arch Intern Med*; 155:211-212, 1995.
106. VANHAELEN M, VANHAELEN-FASTRE R, BUT P, ET AL: Identification of aristolochic acid in Chinese herbs [letter]. *Lancet*; 343:174, 1994.
107. VAN YPERSELE D, STRIHOU C, VANHERWEGHEM JL: The tragic paradigm of Chinese herbs nephropathy [editorial]. *Nephrol Dia Transplant*; 10:157-160, 1995.
108. GORDON DW, ROSENTHAL G, HART J, ET AL: Chaparral ingestion: the broadening spectrum of liver injury caused by herbal medications. *JAMA*; 273:489-490, 1995.
109. SHEIKH NM, PHILEN RM, LOVE LA: Chaparral-associated hepatotoxicity. *Arch Intern Med*; 157:913-919, 1997.
110. MATTEI A, RUEAY P, SAMUEL D, ET AL: Liver transplantation for severe acute liver failure after herbal medicine (*Teucrium polium*) administration [letter]. *J Hepatol*; 22:597, 1995.