

Use of Herbal Supplements and Vitamins in Plastic Surgery: A Practical Review

George Broughton, II,
M.D., Ph.D., Col., M.C.,
U.S.A.

Melissa A. Crosby, M.D.
Jayne Coleman, M.D.
Rod J. Rohrich, M.D.

Dallas, Texas

Learning Objectives: After studying this article, the participant should be able to: 1. Explain what governmental regulations control the labeling and distribution of herbal supplements. 2. List the more commonly used supplements and their reported benefits. 3. List the possible postoperative complications from consumption of the more commonly used herbal supplements. 4. Explain the preoperative management of patients using herbal supplements. 5. Know additional resources to consult when unanswered questions arise.

Background: The American public spends over \$5 billion per year on herbal supplements, and approximately 20 percent of all Americans use prescription medications concurrently with herbal supplements. As the number of people who take alternative medicines rises, there is growing awareness among health care providers of the need to become educated and to educate their patients on the effects that such supplementation may have on their health. As plastic surgeons, we have an added responsibility to become informed because of potential adverse interactions with other medications and anesthesia in the elective surgical patient.

Methods: Literature regarding commonly encountered herbal supplements and vitamins was reviewed and summarized to include reported indications for use and potential adverse effects and interactions specific to the perioperative patient.

Results: Abundant literature exists regarding herbal supplementation, but very little scientific evidence exists to advocate the use of the majority of supplements available on the market. In addition, little is known about the positive and negative interactions that these supplements are capable of producing, and those interactions that are known are based on case reports.

Conclusions: With the lack of quality scientific studies to support the efficacy of most herbal products available and the limited regulation of these products by the government, health care providers are faced with a significant public health dilemma. This article provides a brief overview of information published on commonly encountered herbal supplements and vitamins taken by plastic surgery patients. (*Plast. Reconstr. Surg.* 119: 48e, 2007.)

Widely used today, herbal medicine dates back thousands of years and started in India and China. Chinese medicine dates back approximately 4000 years and is ho-

listic. It is based on the complementary forces *yin* and *yang*. When *yin* and *yang* are in balance, the person is healthy; illness occurs when there is imbalance between the two forces. The Chinese evaluate the interactions between the environment (food, air, and drink) and the body (waste). The cause (and treatment) of the imbalance is determined by examining the tongue, iris, and pulse. Treatment is usually a mixture of herbs, massage, and acupuncture.¹

In India, Ayurvedic medicine dates back to 3000 BC. Ayurvedic medicine combines physiologic and holistic philosophies. It is based on the concept that the human body, like the universe, is composed of five energy elements: earth, water, fire, air, and space. Interaction of these ele-

From the Department of Plastic Surgery, Nancy L & Perry Bass Advanced Wound Healing Laboratory, and the Department of Anesthesia, University of Texas Southwestern Medical Center.

Received for publication December 16, 2005; accepted February 9, 2006.

The opinions or assertions contained herein are the private views of the author and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

Copyright ©2007 by the American Society of Plastic Surgeons

DOI: 10.1097/01.prs.0000252661.72071.8d

ments gives rise to the three *doshas* (forces), seven *dhatu*s (tissues), and three *malas* (waste products). All diseases are attributed to an imbalance among the three *doshas*. Diagnosis is made by an elaborate system of examinations of physical and mental findings. Treatment is then personalized to these findings.^{2,3}

In the United States, herbal therapy began in the colonial days as folk medicine. Women would brew botanicals in the home. Europeans, Chinese, and Native Americans had a significant impact on botanical remedies in the United States. In the nineteenth century, a group of physicians known as Eclectics adopted the holistic practice of herbal medicine.⁴

THE PROBLEM

Complementary and alternative medicine is rarely taught in U.S. medical schools and generally not practiced in U.S. hospitals. Complementary and alternative medicine includes herbal remedies, massage, self-help groups, folk remedies, chiropractic manipulation, relaxation techniques, megavitamins, and others. Astonishingly, the majority of published information about herbal remedies can be located in the nursing and nutritional literature, with a minority in the medical literature.⁵

There are more than 20,000 herbal medicines on the market. Herbal medicine use has increased 380 percent from 1990 to 1997.⁵ A recent survey of 163 health food retail stores in the United States revealed that the top 10 selling herbs are echinacea (*Echinacea purpurea*, *Echinacea pallida*, and *Echinacea angustifolia*), garlic, goldenseal (*Hydrastis canadensis*), 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*).⁶ Current movements 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 agents.⁷ It is estimated that up to 32 to 97 percent of the U.S. population takes herbal remedies on a regular basis.^{8,9} One in seven patients report taking at least one herbal supplement on a weekly basis, and one in five patients report taking one or more herbal medications along with their prescription medicine.¹⁰ Unbelievably, 70 percent of patients do not reveal the use of these supplements to their health care providers.⁸ Among surgical patients, female patients more commonly take herbs (23.6 percent versus 19.2

percent),¹¹ and there is no difference in botanical use between age groups.¹² Herbal use is more prevalent among white, educated, and wealthy individuals.^{11,12} The American Society of Anesthesiologists recommends that all surgical patients stop herbal medications 2 weeks before surgery.¹³

The Government's Responsibility

The U.S. Congress recognized that alternative medicine was becoming more common and in 1992 established the Office of Alternative Medicine through the National Institutes of Health. In 1998, Congress expanded the government's interest by establishing the National Center of Complementary and Alternative Medicine to determine the effectiveness of these therapies and support research in alternative medicine. There are several important differences regarding the manufacturing, health claims, potency, and purity of compounding herbal preparations when compared with other medications. Herbal remedies are not held to the same standards and regulations that the U.S. Food and Drug Administration maintains for the pharmaceutical industry. Phased trials are not required, although the U.S. Food and Drug Administration can "suggest" provision of scientific data to consumers. Individual herbs cannot be patented, although combinations of herbs may be. Although the Dietary Supplement Health and Education Act of 1994 places the burden of product safety assurance on the manufacturer, the U.S. Food and Drug Administration assumes the responsibility of proving that a product is unsafe. Therefore, if the U.S. Food and Drug Administration has reason to believe that an herb is unsafe, it can remove the drug from the market.

Safety and health claim practices continued to be of concern, and the U.S. Food and Drug Administration put forth the "Regulations on Statements Made for Dietary Supplements Concerning the Effects of the Product on the Structure or Function of the Body" to address these concerns. Concerning these regulations, Sabar et al.⁶ explain how herbal manufacturers can sidestep U.S. Food and Drug Administration drug regulations:

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 or func-

tion 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 manufacturers 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.

Why Should You Care?

It has been shown that herbal use is more prevalent among white, educated, and wealthy individuals.^{11,12} This description epitomizes the majority of aesthetic patients and, although there are no comprehensive reports in the literature on herbal supplement use among plastic surgery patients, it is a concern that plastic surgeons cannot ignore.

A general survey¹⁴ of adults on herbal medicine use obtained from three grocery store intercepts in northwest Ohio showed that 40 percent of respondents have used an herbal supplement during the past 12 months. The average number of herbs used was 2.3 per person. The most common reason given for taking herbal supplements is to improve general health (16 percent). Herbal users cited “herbals are natural” as the most common benefit. Magazines (17 percent), health food stores (16 percent), and friends (14 percent) were the most common sources of herbal remedy information. Only 50 percent of the population informed their physician of such use. Forty-one percent used an herbal remedy “sometimes” to “always” to self-treat before seeking medical care from a physician. Fifteen percent of adults treated their children with herbs. Nearly all (86 percent) respondents believed the herb was helpful or very helpful.¹⁴

Although there is no clear evidence that the preoperative use of herbal supplements will cause harmful effects, there are many potential complications that the surgeon should know.¹³ A survey of surgical patients revealed that patients admitted to taking herbal medicines that had coagulation effects (40.5 percent), blood pressure effects (32.7 percent), cardiovascular effects (20 percent), sedative effects (16.7 percent), and effects on electrolytes or diuresis (8.9 percent), and 22.8 percent of patients reported using herbs that are known to cause adverse effects when combined with prescription medications.¹⁵ Another survey of surgery patients found that during the 2 weeks before

surgery, 42.7 percent consumed complementary and alternative medicines: 19.8 percent that inhibit coagulation, 14.4 percent that affect blood pressure, 7.4 percent with cardiac effects, and 8 percent with sedative effects.¹⁶ These concerns have prompted some anesthesiologists and surgeons to postpone elective surgical procedures.¹⁷ A recent survey assessing the knowledge of herbal supplements by anesthesiologists found that only 32 percent answered all questions correctly.¹⁸ Clearly, all physicians need additional and continued training on herbal medicine. Until that time comes, at least one person in the operating room should have practical knowledge of herbal medicine and its effects.

HERBAL SUPPLEMENTS

With over 20,000 herbal medicines available on the market today, discussing only 1 percent of them would be beyond the scope of this article. Eighteen common herbs used frequently by surgery patients are discussed. The 18 herbs are listed in alphabetical order.

Arnica (*Arnica montana*)

Overview

Arnica has been used topically for centuries for its antiinflammatory, analgesic, and antiseptic properties. It is the classic homeopathic remedy for trauma of various kinds and was often used by mountain climbers to relieve sore muscles and minimize bruising from falls. It has also been used for myocarditis, cardiac insufficiency, arteriosclerosis, angina pectoris, and many other unproven applications. There have been multiple clinical studies exploring the efficacy of arnica in reducing postoperative complications. Two randomized, prospective, placebo-controlled trials evaluating liposuction and rhytidectomy demonstrated statistically significant decreases in postoperative swelling and bruising.^{19,20}

Use among Surgical Patients

No data are available.

Synonyms for and Products Containing

Arnica

Leopard’s bane, wolf’s bane, mountain tobacco, Boiron Arnica Montana Cream and Gel, Cosmesis Bruise Away Cream, SinEcch, Vita-Medica, and Arniflora Gel.²¹

Adverse Effects

Arnica is thought²² to be either worthless or dangerous, depending on which form of it was ingested (homeopathic or nonhomeopathic dosages, respectively). Arnica has caused severe and

fatal poisonings, cardiotoxicity, large increases in blood pressure, serious gastrointestinal disturbances, and muscle paralysis.²³ Arnica demonstrates the paradox of homeopathic medicine—the *less* concentrated the drug, the stronger or more efficacious it is. Each time the drug is diluted by a factor of 10 or 100 or more it becomes more potent. That is why the common potencies are available over the counter in the United States and the very highest potencies (most dilute formulations) are reserved for professionals.^{24,25}

Presurgical Precautions and Recommendations

Arnica available in manufactured preparations for the prevention of bruising and swelling can *probably* be safely taken by patients under a physician's supervision. Unsupervised ingestion of arnica should be stopped 2 weeks before surgery and topical arnica (all types) should not be used on broken skin or during the postoperative period until the wound is completely healed.^{24,25}

Bromelain

Overview

Bromelain is an extract derived from the pineapple plant. Proteinases found in bromelain are said to reduce inflammation and swelling after surgery. In addition, bromelain has been shown to act as a potential immunomodulator of tumor cells and as an inhibitor of platelet aggregation.²⁶ Bromelain acts as an immunomodulator by raising the impaired immunocytotoxicity of monocytes against tumor cells and by inducing the production of distinct cytokines such as tumor necrosis factor- α , interleukin-1 β , interleukin-6, and interleukin-8.²⁶

Use among Surgical Patients

No data are available.

Synonyms for and Products Containing Bromelain

Ananas sativus, Ananase, bromeline, Bromelainum, Bromeliaceae, Bromelin, Bromelins, plant protease concentrate, pineapple extract, and Traumanase.²⁷

Adverse Effects

In theory, bromelain may increase the risk of bleeding. Caution is advised in people who have bleeding disorders or who are taking anticoagulants. Bromelain may enhance the antithrombotic activity of such drugs as aspirin. Concomitant use of bromelain and amoxicillin or tetracycline has been reported to increase the serum levels of these antibiotics.²¹ Bromelain may increase heart rate at higher doses and should be used cautiously in

people with heart disease. There are animal data to suggest that bromelain should not be used by patients with liver disease.²⁸

Presurgical Precautions and Recommendations

A randomized, placebo-controlled, double-arm crossover study out of our institution demonstrated oral supplementation with a nutritional supplement containing bromelain, vitamin C, grape seed extract, calcium, and rutin resulted in a 17 percent decrease in wound-healing time, with less inflammation, as compared with the placebo group, without documented bleeding complications.²⁹ Bromelain should be stopped 2 weeks before surgery in a select group of patients taking this supplement with anticoagulants or with a history of bleeding disorder or liver disease.

Dong Quai (*Angelica sinensis*)

Overview

Known as Chinese angelica, dong quai has been used for thousands of years in traditional Chinese, Korean, and Japanese medicine. It remains one of the most popular plants in Chinese medicine, and is used primarily for women's "health conditions." Dong quai has been called "female ginseng," based on its use for gynecologic disorders such as painful dysmenorrhea, postpartum weakness, and general fatigue/low vitality. It is also given for strengthening xue (loosely translated as "the blood"), for cardiovascular conditions/high blood pressure, inflammation, headache, infections, and neuropathic (nerve) pain. Dong quai has multiple coumarin derivatives.^{13,21}

Use among Surgical Patients

Dong quai is taken by 0.9 percent of patients in the perioperative period.¹²

Synonyms for and Products Containing Dong Quai

American angelica, Chinese Danggui, Danggui, Dang Gui, Danggui-Nian-Tong-Tang (DGNTT), European angelica, European Dong Quai, female ginseng, root of the Holy Ghost, Tang Kwei, Tang Quai, Tanggui (Korean), Tanggwi (Korean), Toki (Japanese), wild angelica, wild Chin Quai, women's ginseng, Yuan Nan wild Dong Quai, and Yungui.²⁷

Adverse Effects

Dong quai has been known to prolong prothrombin time/international normalized ratio and activated partial thromboplastin time, and may interact with the effects of Coumadin.³⁰ Increased sun sensitivity with a risk of severe photosensitivity may occur because of chemicals in

dong quai (furocoumarin, psoralen, and bergapten). Safrole, a volatile oil in dong quai, may be carcinogenic (cancer-causing). Long-term use should therefore be avoided, and suntan lotions that contain dong quai often limit the amount of dong quai to less than 1 percent. Dong quai (particularly with prolonged use) is associated with laxative effects/diarrhea, dyspepsia, nausea, vomiting, anorexia, burping, or bloating. Dong quai preparations may contain high levels of sucrose and should be used cautiously by patients with diabetes or glucose intolerance.²⁷

Presurgical Precautions and Recommendations

Patients should stop taking the drug 2 weeks before surgery.

Echinacea (*Echinacea purpurea*, *Echinacea pallida*, *Echinacea angustifolia*)

Overview

Echinacea is used as a natural antibiotic for its immunostimulating properties.³¹ In the United States and Europe, it is taken to prevent and treat upper respiratory tract infections. In the United States, sales of echinacea are believed to represent approximately 10 percent of the dietary supplement market. Echinacea is also purchased to treat genital herpes and radiation-associated toxicity. Topical echinacea juice has been suggested for quicker healing for skin and oral wounds and oral/injectable echinacea for vaginal *Candida albicans* infections.^{32–35}

Use among Surgical Patients

Echinacea is taken by 12.7 percent of surgical patients.¹¹

Synonyms for and Products Containing Echinacea

American coneflower, Echinacin, Echinaforce, Echinaguard, black Sampson, black Susan, cock-up-hat, comb flower, hedgehog, Indian head, Kansas snake root, kegelblume, purple coneflower, red sunflower, rudbeckia, scurvy root, snakeroot, solhat, and sun hat.²⁷

Adverse Effects

Long-term use (8 weeks) is associated with immunosuppression.³⁶ There is a theoretical risk for poor wound healing in chronic users. Echinacea may decrease the effects of cyclosporine and steroids. Echinacea can potentiate the toxicity of barbiturates.³⁷ Other drug–herb interactions include potentiation of hepatotoxic effects of steroids, amiodarone, methotrexate, ketoconazole, and halothane.³⁷ Most of the drug–herb interac-

tions of echinacea occur from the ability of echinacea to inhibit cytochrome CYP3A4³⁸ (Table 1).

Presurgical Precautions and Recommendations

Because of the risk of significant drug–herb interactions, patients should stop taking the drug 2 weeks before surgery.

Ephedra (*Ephedra sinica*, Ma Huang)

Overview

Ephedra, a potent stimulant, is the herbal precursor to epinephrine and pseudoepinephrine. Components of the herb are known to inhibit the complement pathway in vitro,³⁹ raising a concern for prolonged bleeding. In contrast, ephedra has been suspected of creating a hypercoagulable state. Other uses for ephedra include treatment of respiratory illnesses, weight loss, body building enhancer, and as a stimulant. A recent case report⁴⁰ described a weightlifter using an ephedra-containing supplement who had experienced an acute myocardial infarction secondary to thrombosis in situ. All other possible causes of myocardial infarction (including a hypercoagulable state) were ruled out.

Use among Surgical Patients

Ephedra-containing concoctions are consumed by 18 percent of patients preoperatively.⁴¹ The herb is commonly used by the young, the overweight, and female patients.⁴²

Synonyms for and Products Containing Ephedra

Acceleration, AllerClear, AllerPlus, Andro Heat, Better Body Energy for Life, Bio Trim, Biovital Plus, Bladderwrack-Dandelion Virtue, Metabolife 356, Metabolift, Metaboloss, Metabo-TRIM, Naturafed, Naturally Ripped, Naturatussin

Table 1. Herbs That Affect Cytochrome CYP3A4*

Herb and Its Effect	Common Medications Metabolized by CYP3A4†
Induces activity	Coumadin
St. John's wort	Cyclosporine
	Digitalis
Inhibits activity	Lidocaine
Goldenseal	Midazolam
Echinacea	Nifedipine
Licorice	Oral contraceptives
	Testosterone
	Theophylline

*CYP3A4 is the most abundant of all the P450s in human liver and is involved in the metabolism of many environmental toxicants and drugs.

†Data derived from Miller, L. G. (Herbal medicinals: Selected clinical considerations focusing on known or potential drug–herb interactions. *Arch. Intern. Med.* 158: 2200, 1998), and Hu et al. (Herb–drug interactions: A literature review. *Drugs* 65: 1239, 2005).

1, Nettle-Reishi Virtue, Power Thin, ProLab Stoked, Pro-Ripped Ephedra, Respa-Herb, Ripped Fuel, SinuCheck, SinuClear, SnoreStop, Thermadrene, Thermic Blast, Thermicore, Thermo Cuts, ThermoDiet, Ultra Diet Pep, and Xenadrine RFA-1.²⁷

Adverse Effects

According to a recent study based on data from the U.S. Poison Control Centers and sales information, ephedra accounted for 64 percent of all reported adverse effects from herbs.⁴³ Adverse side effects of ephedra-containing drugs include tachycardia, palpitations, angina, seizures, panic attacks, myocardial infarction, hypertension, cerebral vascular accident, arrhythmias, hypertension, and cardiomyopathy.⁴⁴ As of December 30, 2003, the U.S. Food and Drug Administration made a statement that ephedra may present “an unreasonable risk of illness or injury” and mandated the removal of all substances containing ephedra from store shelves.⁴⁵

Presurgical Precautions and Recommendations

Possible intraoperative complications include interactions with anesthetic gases and refractory hypotension requiring phenylephedrine (not pseudoephedrine).⁴¹ Patients taking ephedra-containing supplements should be told to immediately stop using them; patients should be ephedra-free at least 2 weeks before surgery.

Feverfew (*Tanacetum parthenium*)

Overview

Several clinical trials^{46–48} have shown that feverfew reduces the frequency and severity of migraine headaches when taken in small amounts daily. However, analysis⁴⁹ of five double-blind, randomized, controlled trials failed to show any beneficial effect of feverfew over placebo. Feverfew has also been used for arthritis, allergies, cramps, indigestion, postnatal bleeding, painful menstruation, other gynecologic disorders, and intestinal parasites, but its effectiveness for these ailments has never been verified.²¹ Feverfew is regarded as a general tonic, tranquilizer, and “blood purifier.” As a wash or rinse, it is used to prevent infection and reduce swelling from wounds and tooth extraction.

Use among Surgical Patients

No data are available.

Synonyms for and Products Containing Feverfew

Featherfoil, featherfew, flirtwort, bachelor’s buttons, and midsummer daisy.²¹

Adverse Effects

Adverse effects occur most when patients *stop* taking feverfew. People who abruptly discontinue this herb have a 10 percent chance of developing a postfeverfew syndrome—symptoms include rebound headaches, insomnia, muscle stiffness, joint pain, fatigue, nervousness, and tension.²¹

Presurgical Precautions and Recommendations

Feverfew has the potential to interact with Coumadin, has antiplatelet activity,⁵⁰ and has been shown to inhibit lipoxigenase and cyclooxygenase^{51–53} (possibly explaining the beneficial effect this herb *may* have). There are no published recommendations for stopping this drug. Our recommendation is that patients should wean off their feverfew over 2 weeks and then be off it completely for 2 weeks to minimize the risk of developing a postfeverfew syndrome and bleeding.

Garlic (*Allium sativum*)

Overview

Commonly used for cooking, garlic is also used as an antibiotic, diuretic, antihypertensive, lipid-lowering agent, and antitussive. It inhibits platelet aggregation, enhances fibrinolytic activity, and relieves diarrhea.^{31,54–56} Garlic comes in a raw form and as an herbal tablet.

Use among Surgical Patients

Garlic is used in up to 7.9 percent of surgical patients.¹²

Synonyms for and Products Containing Garlic

Ajoene, Allicor, camphor of the poor, clove garlic, garlic clove, garlic corns, garlic extract, garlic oil, Kwai, and Kyolic.²⁷

Adverse Effects

Bad breath, body odor, and allergic reactions are the most common reported side effects of garlic. Fresh garlic has caused rash or skin burns, both in people taking garlic therapy and in food preparers handling garlic. Other side effects include hypotension, headache, and bloating. The most common serious complication from garlic use is increased bleeding secondary to its antiplatelet and antithrombotic effects.^{57–59} Garlic may also prolong the effects of Coumadin. Drug–herb interactions that may occur with garlic include hypoglycemics, cardiovascular medications, and monoamine oxidase inhibitors.

Presurgical Precautions and Recommendations

Patients taking garlic supplements should discontinue its use 7 days before surgery to prevent possible bleeding complications.⁶⁰

Ginger (*Zingiber officinale*)

Overview

Typical uses of ginger include food preparation, relief of respiratory ailments, sore throats, motion sickness, rheumatoid arthritis, postoperative nausea and vomiting, and to dispel evil spirits.^{61,62}

Use among Surgical Patients

Ginger is consumed by 2.6 percent of surgical patients preoperatively.⁶³

Synonyms for and Products Containing

Ginger

African ginger, black ginger, chayenne ginger, cochon ginger, gan jiang, gegibre, gingembre, gingerall, ginger power BP, ginger root, ginger trips, ingwer, Jamaica ginger, kankyo, and race ginger.²⁷

Adverse Effects

Possible perioperative complications include prolonged bleeding (because of inhibition of thromboxane synthetase),⁶⁴ hyperglycemia, and prolonged prothrombin time if taken with Coumadin.⁶⁵

Presurgical Precautions and Recommendations

It is recommended that patients discontinue its use 1 week before surgery.⁶⁰

Ginkgo (*Ginkgo biloba*)

Overview

Ginkgo biloba (maidenhair tree) and its leaf extracts are commonly used to improve circulation,⁶⁶ memory, Alzheimer's disease, and dementia³¹; therefore, it is typically used in the elderly population. Patients also take ginkgo to treat asthma, angina, colds, peripheral vascular disease, cerebral insufficiency, and eye problems.⁶⁷ Ginkgolide B, a constituent of *Ginkgo biloba*, was found to inhibit platelet-activating factor and presumably is the cause of the herb's antiplatelet activities.⁶⁸ The physiologic effects of ginkgo extracts have been reported to include arterial vasodilation, prevention of arterial spasm, reduction of blood viscosity/erythrocyte aggregation, antagonism of platelet-activating factor, and antioxidant capabilities.⁶⁹ Ginkgo also inhibits thromboxane synthetase, which may increase surgical bleeding.⁷⁰

Use among Surgical Patients

Ginkgo is taken by 8.6 percent of surgical patients.¹¹

Synonyms for and Products Containing Ginkgo

Arbre aux quarante écus, Japanbaum, Japanese silver apricot, kew tree, kung sun shu, LI 1370, maidenhair tree, noyer du Japon, oriental plum tree, pei kuo, pei-wen, Rokan, salisburia, *Salisburia adiantifolia*, *Salisburia macrophylla*, sophium, silver apricot, tempeltrae, tanakan, tanakene, tebofortan, tebonin, temple balm, tramisal, valverde, vasan, vital, ya chio, yin-guo, and yin-hsing.²⁷

Adverse Effects

Small clinical trials have not demonstrated bleeding complications with the consumption of ginkgo; however, five cases of spontaneous hemorrhage (four cerebral, one hyphema) and one case of postoperative bleeding after a laparoscopic cholecystectomy have been reported.^{60,71-75} Ginkgo also lowers a patient's seizure threshold and decreases the efficacy of anticonvulsants¹³ and also interacts with monamine oxidase inhibitors.⁷⁶ Ginkgo can interact with barbiturate anesthetics, causing prolonged sedation.⁴¹

Presurgical Precautions and Recommendations

Patients should be advised to cease taking this supplement at least 36 hours before surgery.⁶⁰

Ginseng (*Panax quinquefolius*, *Panax Ginseng*, *Zingiber officinale*)

Overview

Ginseng, most commonly of the Asian or American species, has gained popularity for its alleged ability to protect the body from stress, leading to vitality and longevity. The pharmacologic effects and properties of ginseng are heterogeneous and related to the active constituents known as ginsenosides. Ginsenosides have been shown to decrease blood glucose levels in both type II diabetics and nondiabetics.⁷⁷ Ginsenosides have also been found to inhibit platelet aggregation and enhance fibrinolysis.⁷⁸

Use among Surgical Patients

Ginseng is consumed by 7.4 percent of surgical patients preoperatively.⁶³

Synonyms for and Products Containing Ginseng

Allheilkraut, Araliaceae (family), chikusetsu ginseng, chosen ninjin, dwarf ginseng, five-fingers, five-leaf ginseng, ginseng radix, xi shen, xi yang shen, yakuyo ninjin, yakuyo ninzin, yang

shen yeh-shan-seng, yuan-seng, yuansheng, and zhuzhishen.²⁷

Adverse Effects

Ginseng may cause insomnia, hypoglycemia, hypertension, tachycardia, epistaxis, cerebral arteritis, and headaches.⁷⁹ Ginseng is known to decrease the therapeutic effect of Coumadin,⁸⁰ and paradoxically inhibits platelet adhesiveness and antagonizes platelet-activating factor.⁸¹

Presurgical Precautions and

Recommendations

Ginseng has been studied to determine whether it improves postoperative nausea and vomiting, with mixed results.⁸² There is a case report of a patient undergoing reoperation for postoperative bleeding after a mastectomy, and she had been taking ginseng along with other herbs and medications.⁸³ Other medications that can cause herb–drug interactions include digitalis⁸⁴ and monoamine oxidase inhibitors. Patients should stop taking ginseng 2 weeks before surgery.

Glucosamine Sulfate

Overview

Glucosamine is an amino monosaccharide found in chitin, glycoproteins, and glycosaminoglycans. Available evidence from randomized controlled trials supports the use of glucosamine sulfate in the treatment of osteoarthritis, particularly of the knee. Glucosamine is commonly taken with chondroitin sulfate (a glycosaminoglycan derived from articular cartilage).⁸⁵

Use among Surgical Patients

No data are available.

Synonyms for and Products Containing

Glucosamine Sulfate

Aflexa, Nature's Blend Glucosamine, GS-500, Glucosamine Complex, Maxi GS, and NAG.²¹

Adverse Effects

Glucosamine may increase insulin resistance and consequently affect glucose tolerance. Diabetics should use glucosamine supplements under medical advisement. In theory, glucosamine may increase the risk of bleeding. Caution is advised in patients with bleeding disorders and in those taking drugs that may increase the risk of bleeding.²⁷

Presurgical Precautions and

Recommendations

Glucosamine at a dose of 500 mg three times daily (tablets or capsules) has been well tolerated for 30 to 90 days. In a 3-year study and several short-term trials, the number of adverse events in patients taking glucosamine was no different from placebo.⁸⁶ It appears that glucosamine does not

need to be stopped until the evening before surgery.

Goldenseal (*Hydrastis canadensis*)

Overview

Goldenseal is a Native American medicinal plant introduced to early settlers by Cherokee Indians who used the plant to improve digestion as a bitter tonic and to treat ulcers. An infusion of the root was used as a soothing rinse for eye and skin infections. Goldenseal root has acquired a considerable reputation as a natural antibiotic and as a remedy for various gastric and genitourinary disorders.

Use among Surgical Patients

Goldenseal is consumed by 1.4 percent of surgical patients.¹¹

Synonyms for and Products Containing Goldenseal

Goldenseal, yellow root, eye root, Indian turmeric, jaundice root, eye balm, ground raspberry, and Indian paint.²¹

Adverse Effects

Goldenseal is known to cause sodium depletion and may potentiate the effects of other diuretics.³⁷ It is also known to inhibit cytochrome CYP3A4³⁸ and affects drugs metabolized by the enzyme system (Table 1). Other side effects include gastrointestinal upset, nervousness, and respiratory failure.⁸⁷

Presurgical Precautions and Recommendations

Because goldenseal inhibits cytochrome CYP3A4,³⁸ patients should stop taking this drug 2 weeks before surgery.

Grape Seed

Overview

Grape seed is extracted from red and purple grapes and purported as having health benefits based on its antioxidant action found in its active proanthocyanidin content. Proanthocyanidin is a bioflavonoid that acts as a strong antioxidant, protecting DNA from harmful free radicals. In addition, grape seed extract has been reported to reduce inflammation, stabilize collagen and elastin, act as a natural antihistamine, and protect and heal connective tissue, and has chemopreventive effects in patients with cancer.⁸⁸ Reportedly, grape seed extract provides two to five times better protection against oxidative tissue damage as compared with vitamins C and E singly and in combination.⁸⁹

Use among Surgical Patients

No data are available.

Synonyms for and Products Containing Grape Seed

Opc (Oligomeric Proanthocyanidins), Opc 85, and grape seed extract.²¹

Adverse Effects

Grape seed extract appears safe overall; however, as with any supplement, adequate scientific studies have not been performed to delineate the beneficial and adverse effects associated with this supplement.

Presurgical Precautions and Recommendations

None.

Kava Kava (*Piper methysticum*)**Overview**

Kava kava is typically used for its antianxiety (kava potentiates γ -aminobutyric acid) and muscle relaxant properties.¹³

Use among Surgical Patients

Kava kava is taken by 1.2 percent of surgical patients.^{31,63}

Synonyms for and Products Containing Kava Kava

Ava, ava pepper, awa, intoxicating pepper, kava, kava kava, kawa, kew, rauschpfeffer, sakau, tonga, wurzelstock, and yanggona.⁹⁰

Adverse Effects

Kava kava can prolong the anesthetic effects of barbiturate anesthetics¹³ and has been shown in vitro to cause platelet dysfunction through inhibition of thromboxane synthesis.⁹¹ A man taking kava kava with alprazolam became semicomatose.⁹² Kava kava-containing products have been associated with liver-related injuries—including hepatitis, cirrhosis, and liver failure—in over 25 reports of adverse events in other countries. Four patients required liver transplants. In the United States, the U.S. Food and Drug Administration has received a report of a previously healthy young woman who required liver transplantation, in addition to several reports of liver-related injuries.⁹⁰ Kava kava also has an antagonistic effect on dopamine. Patients taking levodopa-based medication for Parkinson's disease should not take this drug.^{93,94}

Presurgical Precautions and Recommendations

Patients should stop taking kava kava 2 weeks before surgery.

Licorice (*Glycyrrhiza glabra*)**Overview**

Licorice root has long been known for its ability to soothe respiratory inflammation. Licorice extract is a proven treatment for stomach ulcers. The extract also seems to have a beneficial effect on viral infections of the liver. In Asian medicine, the root has also been used for boils, dehydration, diarrhea, eye diseases, headache, sore throat, and swelling from infections. Licorice contains glycyrrhetic acid, which is known to heal stomach ulcers. Other ingredients—including glabridin, glycyrrhizin, and licoricidin—are antiinflammatory. The glycyrrhizin in licorice also appears to be effective against viruses such as hepatitis B, influenza, and human immunodeficiency virus by enhancing the immune system's T-cell count and stimulating interferon.²¹

Use among Surgical Patients

Licorice is taken by 0.8 percent of surgical patients.¹¹

Synonyms for and Products Containing Licorice

Black sugar, licorice root, liquorice, sweetroot, and sweetwood.²¹

Adverse Effects

Licorice is known to cause hypertension, arrhythmias, and sodium retention. In addition, licorice causes hypokalemia, which may be magnified by diuretic use, and has resulted in cardiac arrest.⁹⁵ Licorice inhibits CYP3A4 in vitro and may affect the metabolism of drugs (Table 1) metabolized through this cytochrome.³⁸ It is sometimes accompanied by fatigue, headaches, and myalgias. Licorice inhibits platelet aggregation and contains coumarin. Because of the possibility of these side effects, licorice preparations should not be used longer than 6 weeks. The side effects disappear after the drug is discontinued.²¹

Presurgical Precautions and Recommendations

At recommended dosage levels, licorice is unlikely to produce any side effects. However, when taken in high dosages (>20 g of licorice extract or 50 g of licorice root daily) for an "extended period of time," it will lead to adverse effects listed above. Patients should stop taking licorice 2 weeks before surgery.

Omega-3 Fatty Acids**Overview**

Omega-3 fatty acids are found in various fish, canola oil, flaxseed oil, walnuts, and green leafy vegetables. The first discovery of the health ben-

efits of omega-3 fatty acids was made in the 1970s, when scientists discovered that the Eskimos living in Greenland had fewer occurrences of cardiovascular disease, rheumatoid arthritis, diabetes mellitus, and psoriasis.⁹⁶ Reported physiologic effects of omega-3 fatty acids include reduction of cholesterol, reduction of blood clots, decreased inflammation and pain, alleviation of fatigue and depression, and prevention of breast cancer.^{96,97}

Use among Surgical Patients

No data are available.

Synonyms for and Products Containing Omega-3 Fatty Acids

#945;linolenic acid (ALA, C18:3n-3), alpha-linolenic acid, cod liver oil, cold water fish, docosahexaenoic acid (DHA, C22:6n-3), eicosapentaenoic acid (EPA, C20:5n-3), fish oil fatty acids, fish body oil, fish liver oil, fish extract, halibut oil, and long chain polyunsaturated fatty acids.²⁷

Adverse Effects

Intake of 3 g/day or greater of omega-3 fatty acids may increase the risk of bleeding, although there is little evidence of significant bleeding risk at lower doses.⁹⁸⁻¹⁰⁰ Very large intakes of fish oil/omega-3 fatty acids (“Eskimo” amounts) may increase the risk of hemorrhagic (bleeding) stroke.¹⁰¹ High doses have also been associated with nosebleed and blood in the urine.¹⁰² Fish oils appear to decrease platelet aggregation and prolong bleeding time and increase fibrinolysis (breaking down of blood clots), and may reduce von Willebrand factor.¹⁰³

Presurgical Precautions and Recommendations

Because of the ability of omega-3 fatty acids to reduce blood clot formation, patients should use caution taking supplements containing omega-3 fatty acids before surgical intervention. Patients taking 3 g or more per day should stop taking omega-3 fatty acid supplements 2 weeks before surgery.

Saw Palmetto (*Serenoa repens*, *Sabal serrulata*)

Overview

Popular in Europe, it is used for symptoms associated with benign prostatic hypertrophy. Although not considered the standard of care in the United States, it is the most popular herbal treatment for this condition.¹³

Use among Surgical Patients

Approximately 2.3 percent of surgical patients use saw palmetto.¹² The majority of patients using saw palmetto are male.

Synonyms for and Products Containing Saw Palmetto

American dwarf palm tree, Arecaceae (family), cabbage palm, dwarf palm, Elusan Prostate, saw palmetto berryserenoa, *Serenoa repens*, Stro-gen, WS 1473, and *Zwegpalme*.²⁷

Adverse Effects

Saw palmetto can cause occasional gastric distress, tachycardia, and angina.¹³ The active ingredients or the mechanism by which they act are not well defined. There has been one report of severe intraoperative bleeding in a patient taking saw palmetto.¹⁰⁴ In addition, there are theoretical drug-herb interactions with phenylephrine, norepinephrine, propranolol, amiloride, and actinomycin D.⁸⁷

Presurgical Precautions and Recommendations

Because of the risk of postoperative bleeding, patients should stop taking the drug 2 weeks before surgery.

St. John’s Wort (*Hypericum perforatum*)

Overview

St. John’s wort is used to treat depression and anxiety by inhibiting serotonin, norepinephrine, and dopamine reuptake by neurons¹⁰⁵ and has been found to be as efficacious as monoamine oxidase inhibitors.¹⁰⁶ St. John’s wort has also been shown to induce the cytochrome P450 pathway, altering the metabolism of many drugs metabolized through this pathway.

Use among Surgical Patients

St. John’s wort is taken by up to 4.5 percent of surgical patients.¹²

Synonyms for and Products Containing St. John’s Wort

Amber touch-and-heal, balm-of-warrior’s wound, balsana, bassant, Blutkraut, bossant, corancillo dendlu, devil’s scorge, Eisenblut, flor de Sao Joa, fuga daemonum, goatweed hartheu, and witcher’s herb.²⁷

Adverse Effects

Potential side effects include prolonged postoperative sedation. This tranquilizing effect may be more severe when combined with narcotics; however, there have been no reports of this to date.¹⁵ Long-term use of the herb has been associated with cardiovascular collapse on induction of anesthesia.¹⁰⁷ St. John’s wort is known to induce the activity of hepatic cytochrome CYP3A4¹⁰⁸ and reduce the efficacy of cyclosporine, digitalis, Coumadin, oral contraceptives,

indinavir, theophylline,^{109–111} midazolam, and lidocaine.³⁷

Presurgical Precautions and Recommendations

St. John's wort (*Hypericum perforatum*) is used by many patients to treat depression and anxiety by exerting its effects by inhibiting serotonin, norepinephrine, and dopamine reuptake by neurons.¹⁰⁵ Caution should be exercised by patients using antidepressants containing serotonin and by those taking monoamine oxidase inhibitors. St. John's wort has also been shown to induce the cytochrome P450 pathway, altering the metabolism of many drugs (most notably in our patients, midazolam and lidocaine) metabolized through this pathway (Table 1). In addition, reported photosensitivity related to the compound hypericin has been described.¹¹² Patients taking other photosensitizing agents such as tetracycline, doxycycline, and specifically retinoids such as tretinoin used by many plastic surgery patients should be avoided. It has been recommended that patients discontinue all use of St. John's wort 2 weeks before surgery.⁵⁴

Valerian Root (*Valeriana officinalis*)

Overview

Valerian root is used commonly for its sedative and hypnotic properties in patients with insomnia, and less commonly as an anxiolytic.¹¹³ Multiple preparations are available (a dried herb, an aqueous extract, or an ethanol extract¹³), and the herb is commonly combined with other herbal medications.

Use among Surgical Patients

Valerian root is taken by 2.5 percent of surgical patients.¹²

Synonyms for and Products Containing Valerian Root

Garden heliotrope, tobacco root, All-heal, Amantilla, capon's tail, heliotrope, setwall, and vandal root.²¹

Adverse Effects

The herb may cause excessive sedation and muscle relaxation through interactions with γ -aminobutyric acid receptors. Concomitant use with barbiturates is contraindicated.¹³ Additional side effects include gastric distress, blurred vision, excitability, restlessness, and acute hepatitis.¹¹⁴ Long-term consumption of valerian root by one patient resulted in delirium and cardiac failure during emergence from general anesthesia, presumably secondary to withdrawal.¹¹⁵ Administra-

tion of benzodiazepines will reverse the patient's symptoms.

Presurgical Precautions and Recommendations

Because valerian root may potentiate sedative effects of barbiturates, anesthetics, and central nervous system depressants, patients should stop taking the drug 2 weeks before surgery.

Many commonly encountered supplements have the potential to interact with prescription medications and anesthetics used during surgery. Few studies exist examining these interactions, and the majority of this information has been identified through case-by-case reporting. Because 16 percent of adults in the United States report the use of herbal supplements with one or more prescription medications, it is prudent that plastic surgeons be aware of some of the most common supplement–drug interactions.¹¹⁶ Because of the lack of consensus on the interaction between herbal supplements and anesthetics, the American Society of Anesthesiologists recommends that all herbal medications be stopped 2 to 3 weeks before an elective operative procedure. Many supplements and vitamins may be stopped later. However, because of the lack of content consistency in marketed products, we support this recommendation for our patients. Table 2 provides a brief overview of some recently identified interactions.^{93,94,117}

VITAMINS

Only the vitamins that may have a significant impact on surgical patient care are discussed. Vitamins A, B₁₂, C, and E are discussed.

Vitamin A (Retinoic Acid)

Overview

Vitamin A is a generic term for a large number of related compounds including retinol, retinal, retinoic acid, and other retinoids. Retinal is converted to retinoic acid in the body and plays a role in gene transcription. Beta-carotene and other carotenoids are found in various plants that ultimately are converted to retinol in the body. Vitamin A plays a role in vision, immunity, gene transcription, red blood cell production, growth, and embryologic development.¹¹⁸ Brief, high doses of vitamin A may improve wound healing and counteract the negative effects of chronic corticosteroid use and irradiation.^{119–122}

Use among Surgical Patients

From 15.1 percent¹² to 51 percent¹¹ of preoperative patients report taking vitamins.

Table 2. Supplement–Drug Interactions

Supplement	Drug	Interaction
Garlic	Warfarin	Increased INR
	Chlorpropamide	Hypoglycemia
	ASA/NSAIDs	Potentiate antiplatelet effects
<i>Ginkgo biloba</i>	Antihypertensives	Potentiate effects
	Warfarin/ASA	Bleeding
	Anticonvulsants	Decrease effectiveness
	Thiazide diuretics	Increase BP
	Trazodone	Coma
St. John's wort	Digoxin	Increased plasma levels
	SSRIs/MAO inhibitors	Central serotonin excess
	Oral contraceptives	Altered menstrual bleeding
	Loperamide	Acute delirium episode
	Warfarin	Decreased INR
	Digoxin, theophylline, amitriptyline, indinavir, cyclosporine, estrogen	Decreased plasma levels
Ginseng	Alcohol	Increased blood concentrations
	Warfarin	Decreased INR
	Phenelzine	Insomnia, headache, tremulousness, mania
Echinacea	No known	No known
Kava	Alprazolam	Coma
Feverfew	ASA/anticoagulants	Potentiate effects

INR, international normalized ratio; ASA, acetylsalicylic acid; NSAIDs, nonsteroidal antiinflammatory drugs; BP, blood pressure; SSRIs, serotonin selective reuptake inhibitors; MAO, monoamine oxidase.

See text for detailed explanation. Adapted from Hu, Z., Yang, X., Ho, P. C., et al. Herb-drug interactions: A literature review. *Drugs* 65: 1239, 2005.

Synonyms for and Products Containing Vitamin A

Antixerophthalmic vitamin, axerophtholum, beta-carotene oleovitamin A, retinaldehyde, retinyl acetate, retinyl palmitate, Aquasol A, Palmilate-A, and Solatene.²⁷

Adverse Effects

Recommended dietary allowance levels for vitamin A oral intake have been established by the U.S. Institute for Medicine of the National Academy of Sciences to prevent deficiencies in vitamin A. At recommended doses [900 µg/day (3000 IU) for men; 700 µg/day (2300 IU) for women],²⁷ vitamin A is generally considered nontoxic. Excess dosing may lead to acute or chronic toxicity. Toxicity has been shown to result in liver damage, hemorrhage, and coma, and excess amounts can lead to increased risk of congenital disabilities in pregnant women.¹¹⁸

Presurgical Precautions and Recommendations

Patients taking their recommended daily dose of vitamin A do not need to stop taking it before surgery. Patients exceeding the recommended dietary allowance (>5000 IU/day) should be discouraged from taking such high doses unless under the supervision of a physician.

Vitamin B₁₂ (Cyanocobalamin)

Overview

Vitamin B₁₂ is an essential water-soluble vitamin that is commonly found in a variety of foods

such as fish, shellfish, meats, and dairy products. Vitamin B₁₂ is frequently used in combination with other B vitamins in a vitamin B complex formulation. The human body stores several years' worth of vitamin B₁₂, so nutritional deficiency of this vitamin is extremely rare. Vitamin B₁₂ is bound to the protein in food. Hydrochloric acid in the stomach releases B₁₂ from protein during digestion. Once released, B₁₂ complexes with intrinsic factor and is absorbed into the bloodstream. The elderly are the most at risk for deficiency.¹²³ Vitamin B₁₂ deficiency is seen with pernicious anemia (from decreased intrinsic factor production) and in strict vegetarians who do not consume animal proteins.¹²⁴ The recommended dietary allowances is 2.4 mg/day for adults and adolescents aged 14 years and older.

Use among Surgical Patients

From 15.1 percent¹² to 51 percent¹¹ of preoperative patients report taking vitamins.

Synonyms for and Products Containing Vitamin B₁₂

B-12, B complex, B complex vitamin, bedumil, cobalamin, cobalamins, cobamin, cyanocobalamin, cyanocobalaminum, cycobemin, hydroxocobalamin, hydroxocobalaminum, hydroxocobemine, idrossocobalamina, methylcobalamin, vitadurin, Alphamin, Anacobin, Bedoz, Cobex, Cobolin-M, Crystamine, Cryst, Cyanoject, and Cyomin.²¹

Adverse Effects

Itching, rash, transitory exanthema, and urticaria have been reported. Vitamin B₁₂ (20 µm/

day) and pyridoxine (80 mg/day) have been associated with cases of rosacea fulminans.¹²⁵ Symptoms may persist for up to 4 months after the supplement is stopped and may require treatment with systemic corticosteroids and topical therapy. Peripheral vascular thrombosis has been reported.

Presurgical Precautions and Recommendations

Vitamin B₁₂ taken at the recommended dose does not need to be stopped before surgery. A recent study¹²⁶ measured vitamin B₁₂, folate, creatinine, and albumin concentrations in 101 consecutive patients with venous thrombotic disease and 101 control subjects, matched for age and sex. Serum vitamin B₁₂ concentrations were significantly lower in patients with venous thrombotic disease than in the control subjects. It is thought that this may have been caused by an accumulation of homocysteine, which is believed to cause intimal thickening and induce a hyperthrombotic state.¹²⁷⁻¹³⁰ Hyperhomocysteinemia is thought to be responsible for accelerated atherosclerosis and venous thromboembolic disease.^{126,131-133} Patients deficient of these vitamins *might* be at increased risk of flap failure for similar reasons (speculation).

Vitamin C (Ascorbic Acid)

Overview

Vitamin C is required for the synthesis of collagen and plays an important role in the synthesis of the neurotransmitter norepinephrine. Vitamin C is also an effective antioxidant and has been shown to be able to regenerate other antioxidants such as vitamin E. Vitamin C is often taken to prevent the common cold; however, controlled, double-blind, clinical trials have shown minimal effects on the common cold.^{134,135} In addition, vitamin C has been shown to have no significant effect on outcome between terminal cancer patients taking vitamin C versus placebo.¹³⁶

Use among Surgical Patients

From 15.1 percent¹² to 51 percent¹¹ of preoperative patients report taking vitamins.

Synonyms for and Products Containing

Vitamin C

Antiscorbutic vitamin, ascorbate, ascorbic acid, ascorbyl palmitate, calcium ascorbate, cevitamic acid, iso-ascorbic acid, and sodium ascorbate. Vitamin C is included in thousands of multivitamin formulations. Vitamin C products in the United States include Ascorbicap, C-500-GR, Cecon, Cetane, Cevalin, Ce-Vi-Sol, Cevi-Bid, C-Gram, Ce-Vi-Sol, Il-C, Dull-C, and Flavorcee, Vita-C. Ca-

nadian products include Proflavanol C and Revitalose C-1000.²⁷

Adverse Effects

The recommended daily intake of vitamin C is 60 mg. The tolerable upper intake level is reported to be 2000 mg/day as reported by the Institute of Medicine. Upper tolerable intake levels “represent the maximum intake of a nutrient that is likely to pose no risk of adverse health effects in almost all individuals in the general population.”¹³⁷ High doses of vitamin C have been associated with multiple adverse effects, particularly at doses greater than 2000 mg/day. Large doses may precipitate hemolysis (red blood cell destruction) in patients with glucose 6-phosphate dehydrogenase deficiency. High doses of vitamin C should be avoided in people with conditions aggravated by acid loading, such as cirrhosis, gout, renal tubular acidosis, or paroxysmal nocturnal hemoglobinuria.^{138,139}

Presurgical Precautions and Recommendations

Patients taking vitamin C supplementation do not necessarily have to stop their intake during the perioperative period.

Vitamin E (Tocopherol)

Overview

Vitamin E is a fat-soluble vitamin with antioxidant properties. Vitamin E exists in eight different forms, of which α -tocopherol is the most active form in humans. Dosing and daily allowance recommendations for vitamin E are often provided in α -tocopherol equivalents to account for the different biological activities of the various forms of vitamin E, or in international units, which food and supplement labels may use. For conversion, 1 mg of α -tocopherol equivalents = 1.5 IU. Vitamin E supplements are available in natural or synthetic forms. The natural forms are usually labeled with the letter “d” (for example, d-gamma-tocopherol), whereas synthetic forms are labeled “dl” (for example, dl-alpha-tocopherol). Vitamin E has been proposed for the prevention or treatment of numerous health conditions, often based on its antioxidant properties and as a free radical scavenger. However, aside from the treatment of vitamin E deficiency (which is rare), there are no clearly proven medicinal uses of vitamin E supplementation beyond the recommended daily allowance. There is ongoing research in numerous diseases, particularly in cancer and heart disease.^{140,141}

Use among Surgical Patients

From 15.1 percent¹² to 51 percent¹¹ of preoperative patients report taking vitamins.

Synonyms for and Products Containing Vitamin E

Spondyvit, tocopherol, tocotrienol, tocotrienol concentrate, tocopheryl succinate, Amino-Opti-E, Aquasol E, Aquasol E, E-Complex-600, Liqui-E, Pheryl-E, Vita Plus E, Webber Vitamin E, Alph-E, Vitamin E-d-Alpha, Vitamin E-dl Alpha, E Mixed, Vitamin E Dry, Total E, Vitamin E MTC, Nutr-E-Sol, Aquasol E, Aquavit-E, Liquid E, E-Pherol, and Dry E.^{21,27}

Adverse Effects

Recent evidence suggests that regular use of high-dose vitamin E supplements (400 IU/day or greater) may increase the risk of death (all-cause mortality risk difference in high-dosage vitamin E trials was 39 per 10,000 persons).¹⁴² These conclusions have been criticized by some experts because they are based on recalculations (meta-analyses) of the results of prior smaller studies that were of mixed quality, with variable results, and often in patients with chronic illnesses. High doses of vitamin E (>400 IU/day) might increase the risk of bleeding because of inhibition of platelet aggregation and antagonism of vitamin K–dependent clotting factors (particularly in patients with vitamin K deficiency).^{143–145} In studies of vitamin E, a small increase in the rate of hemorrhagic stroke and gum bleeding has been observed, particularly when used in humans with aspirin.¹⁴⁶ Increased risk of bleeding when used with warfarin (Coumadin) has been noted.^{147,148} However, others have not observed a greater incidence of bleeding.¹⁴⁹ Caution is advised in patients with bleeding disorders and in those taking drugs that may increase the risk of bleeding.

Presurgical Precautions and Recommendations

Patients should discontinue high doses of vitamin E (>400 IU/day) 2 to 3 weeks before surgery.

DISCUSSION

Herbs, vitamins, and minerals have been used for centuries not only to supplement the diet but also to treat illness and improve health. Annual sales of dietary supplements in the United States are approaching \$6 billion, and an average of 1000 new products are being developed each year. Despite the fact that one-quarter of adults reported using an herbal product to treat an illness last year, limited evidence from randomized controlled trials exists to support the efficacy of the majority of the herbal supplements available to the public. In addition, Bent and Ko¹⁵⁰ report that of the 10 most commonly used herbs in the United States in 2001, statistically significant evidence of efficacy exists

only for garlic, ginkgo biloba, saw palmetto, and St. John’s wort. As demonstrated by this systematic review, additional research is needed to define further the benefits and risks of presently available dietary supplements.

The Dietary Supplement Health and Education Act of 1994 classified herbs as “dietary supplements” and exempted them from the safety and efficacy requirements and regulations that prescription and other over-the-counter medications must fulfill. In addition, the burden was placed on the U.S. Food and Drug Administration to prove a supplement unsafe before its removal from store shelves.¹⁵¹ Therefore, manufacturers are not obligated to guarantee the quality or quantity of herbal substance in their products, resulting in the problem of batch-to-batch variability. As with any public market, the buyer must beware.

As consumers and health care providers, we have a responsibility to educate ourselves and our patients about the risks and potential benefits of such supplements. We must inquire about over-the-counter medications, including vitamin and herbal supplementation, in our preoperative interviews. Until more stringent regulations exist and further research is performed, we must remember that because something is “natural” does not always mean it is safe.

Table 3. Potential Positive and Negative Effects of Common Vitamins

Vitamin	Positive	Negative
Vitamin A	Vision Immunity Development RBC production	Liver toxicity Bleeding Birth defects
Vitamin E	Antioxidant Wound healing	Anticoagulant
Vitamin C	Antioxidant Collagen synthesis Norepinephrine synthesis	Kidney stones GI distress
Vitamin D	Bone formation/mineralization Intestinal Ca ²⁺ absorption	Anorexia Nausea/vomiting Impaired renal function Metastatic calcifications
Vitamin B ₆	CNS Skin metabolism Erythropoiesis	Balance difficulties Nerve injury (decreased sensation)
Vitamin B ₁₂	Prevents anemia	Rash

RBC, red blood cells; GI, gastrointestinal; CNS, central nervous system.

To adequately cover such a vast topic in one setting is impossible. In this discussion, we hope to have provided those in practice a brief guide to commonly encountered dietary supplements that we have seen consumed by our patient population. Tables 3 and 4 summarize the above-mentioned herbal supplements and vitamins. Below, we have provided a brief list of additional resources to assist in educating ourselves and our patients.

Additional Resources

PDR for Herbal Medicines

National Institutes of Health Office of Dietary Supplements: <http://dietary-supplements.info.nih.gov/>

U.S. Food and Drug Administration Center for Food Safety and Applied Nutrition: www.vf.cfsan.fda.gov

Table 4. Potential Positive and Negative Effects of Common Supplements

Supplement	Positive	Negative
Arnica	Antiinflammatory Analgesic Antiseptic	? Increased bleeding
Bromelain	Decreases bruising Antiinflammatory Immunity Platelet inhibitor Wound healing	Platelet inhibitor
Dong quai	Gynecologic disorders	Bleeding Photosensitivity Gastrointestinal problems
Echinacea	Antibiotic Wound healing	Immunosuppression (long-term use) Drug interactions (inhibits cytochrome P450)
Ephedra	Stimulant Decongestant Appetite suppressor	Hypertension Tachycardia Palpitations Irritability
Feverfew	Migraine headaches	Bleeding Postfeverfew syndrome (when stopped abruptly)
Garlic	Decreases BP Antithrombotic Antihyperlipidemic	? Increased bleeding
Ginger	Relief of URI Relief of sore throat Arthritis Motion sickness	Bleeding Interacts with Coumadin Hyperglycemia
<i>Ginkgo biloba</i>	Antioxidant Anticoagulant Vasodilation	Vasodilation Drug interactions [lowers seizure threshold; interacts with MOA inhibitors; prolonged sedation (barbiturates)]
Ginseng	Hypoglycemic Anticoagulant Stress relief	Anticoagulant Hypoglycemia Hypertension Tachycardia Unknown
Glucosamine sulfate	Arthritis	Unknown
Goldenseal	Dyspepsia Antibiotic	Drug interactions (inhibits cytochrome P450)
Grape seed extract	Antioxidant Antihistamine Chemo protective Wound healing	Unknown
Kava kava	Antianxiety Muscle relaxant	Prolong anesthesia Liver injury (hepatitis, cirrhosis, liver failure)
Licorice	Respiratory inflammation Dyspepsia	Increased bleeding (inhibits platelet aggregation) Drug interactions (inhibits cytochrome P450)
Omega-3 fatty acids	Reduce cholesterol Anticoagulant Antiinflammatory	Anticoagulant
Saw palmetto St. John's wort	Benign prostatic hypertrophy Antidepressant	? Increased bleeding Photosensitivity Inducing cytochrome P450
Valerian root	Sedative	Potentiates sedation

BP, blood pressure; URI, upper respiratory infection; MAO, monoamine oxidase.

Food and nutrition information center: www.nal.usda.gov
 Institute of Medicine

Rod J. Rohrich, M.D.

Department of Plastic Surgery
 University of Texas Southwestern Medical Center
 5323 Harry Hines Boulevard, Suite E7.210
 Dallas, Texas 75390-9132
rod.rohrich@utsouthwestern.edu

DISCLOSURE

None of the authors has a financial interest in any of the products, devices, or drugs mentioned in this article.

REFERENCES

- Latchman, Y., Whittle, B., Rustin, M., Atherton, D. J., and Brostoff, J. The efficacy of traditional Chinese herbal therapy in atopic eczema. *Int. Arch. Allergy Immunol.* 104: 222, 1994.
- Dattner, A. M. Herbal and complementary medicine in dermatology. *Dermatol. Clin.* 22: 325, 2004.
- Routh, H. B., and Bhowmik, K. R. Traditional Indian medicine in dermatology. *Clin. Dermatol.* 17: 41, 1999.
- Bedi, M. K., and Shenefelt, P. D. Herbal therapy in dermatology. *Arch. Dermatol.* 138: 232, 2002.
- Ernst, E. Harmless herbs? A review of the recent literature. *Am. J. Med.* 104: 170, 1998.
- Sabar, R., Kaye, A. D., and Frost, E. A. Perioperative considerations for the patient on herbal medicines. *Middle East J. Anesthesiol.* 16: 287, 2001.
- Winslow, L. C., and Kroll, D. J. Herbs as medicines. *Arch. Intern. Med.* 158: 2192, 1998.
- Eisenberg, D. M., Kessler, R. C., Foster, C., Norlock, F. E., Calkins, D. R., and Delbanco, T. L. Unconventional medicine in the United States: Prevalence, costs, and patterns of use. *N. Engl. J. Med.* 328: 246, 1993.
- Brown, J. S., and Marcy, S. A. The use of botanicals for health purposes by members of a prepaid health plan. *Res. Nurs. Health* 14: 339, 1991.
- Eisenberg, D. M., Davis, R. B., Ettner, S. L., et al. Trends in alternative medicine use in the United States, 1990–1997: Results of a follow-up national survey. *J.A.M.A.* 280: 1569, 1998.
- Tsen, L. C., Segal, S., Pothier, M., and Bader, A. M. Alternative medicine use in presurgical patients. *Anesthesiology* 93: 148, 2000.
- Leung, J. M., Dzankic, S., Manku, K., and Yuan, S. The prevalence and predictors of the use of alternative medicine in presurgical patients in five California hospitals. *Anesth. Analg.* 93: 1062, 2001.
- Tessier, D. J., and Bash, D. S. A surgeon's guide to herbal supplements. *J. Surg. Res.* 114: 30, 2003.
- Martin, K. J., Jordan, T. R., Vassar, A. D., and White, D. B. Herbal and nonherbal alternative medicine use in Northwest Ohio. *Ann. Pharmacother.* 36: 1862, 2002.
- Norred, C. L. A follow-up survey of the use of complementary and alternative medicines by surgical patients. *A.A.N.A. J.* 70: 119, 2002.
- Wren, K. R., Kimbrall, S., and Norred, C. L. Use of complementary and alternative medications by surgical patients. *J. Perianesth. Nurs.* 17: 170, 2002.
- Murphy, J. M. Preoperative considerations with herbal medicines. *A.O.R.N. J.* 69: 173, 1999.
- Lennox, P. H., and Henderson, C. L. Herbal medicine use is frequent in ambulatory surgery patients in Vancouver, Canada. *Can. J. Anaesth.* 50: 21, 2003.
- Kulik, M. *Arnica montana* in the reduction of ecchymosis and edema in liposuction. Presented at the 35th Annual Meeting of the American Society for Aesthetic Plastic Surgery, Las Vegas, Nevada, April 27–May 3, 2002.
- Seeley, B. Homeopathic *Arnica montana* in the reduction of ecchymosis after facelift. Presented at the Spring Meeting of the American Academy of Facial Plastic and Reconstructive Surgery, New York, 2002.
- Drug Profiles. In *Physician's Desk Reference*. Montvale, N.J.: Thomson PDR, 2005.
- Daane, S. P. Potential for danger with *Arnica montana*. *Ann. Plast. Surg.* 46: 349, 2001.
- Lawrence, W. T. *Arnica*. *Plast. Reconstr. Surg.* 112: 1164, 2003.
- Riley, D. *Arnica montana* and homeopathic dosing guidelines. *Plast. Reconstr. Surg.* 112: 693, 2003.
- Pechter, E. A. *Arnica montana* and dosing of homeopathic medication. *Plast. Reconstr. Surg.* 114: 260, 2004.
- Maurer, H. R. Bromelain: Biochemistry, pharmacology and medical use. *Cell Mol. Life Sci.* 58: 1234, 2001.
- Drug Information and Supplement Information. Available at: <http://www.mayoclinic.com/health/drug-information/DrugHerbIndex>. Accessed December 3, 2005.
- Shibayama, Y. An experimental study into the cause of acute haemorrhagic gastritis in cirrhosis. *J. Pathol.* 149: 307, 1986.
- Brown, S. A., Coimbra, M., Coberly, D. M., Chao, J. J., and Rohrich, R. J. Oral nutritional supplementation accelerates skin wound healing: A randomized, placebo-controlled, double-arm, crossover study. *Plast. Reconstr. Surg.* 114: 237, 2004.
- Jazieh, A. R., and Khalil, M. Hematologic complications of alternative remedies. *Int. J. Hematol.* 74: 405, 2001.
- Mitka, M. FDA never promised an herb garden: But sellers and buyers eager to see one grow. *J.A.M.A.* 280: 1554, 1998.
- Barak, V., Birkenfeld, S., Halperin, T., and Kalickman, I. The effect of herbal remedies on the production of human inflammatory and anti-inflammatory cytokines. *Isr. Med. Assoc. J.* 4: 919, 2002.
- Barrett, B., Vohmann, M., and Calabrese, C. Echinacea for upper respiratory infection. *J. Fam. Pract.* 48: 628, 1999.
- Barrett, B. Medicinal properties of *Echinacea*: A critical review. *Phytomedicine* 10: 66, 2003.
- Vonau, B., Chard, S., Mandalia, S., Wilkinson, D., and Barton, S. E. Does the extract of the plant *Echinacea purpurea* influence the clinical course of recurrent genital herpes? *Int. J. STD AIDS* 12: 154, 2001.
- Boullata, J. I., and Nace, A. M. Safety issues with herbal medicine. *Pharmacotherapy* 20: 257, 2000.
- Miller, L. G. Herbal medicinals: Selected clinical considerations focusing on known or potential drug-herb interactions. *Arch. Intern. Med.* 158: 2200, 1998.
- Budzinski, J. W., Foster, B. C., Vandenhoeck, S., and Arnaon, J. T. An in vitro evaluation of human cytochrome P450 3A4 inhibition by selected commercial herbal extracts and tinctures. *Phytomedicine* 7: 273, 2000.
- Ling, M., Piddlesden, S. J., and Morgan, B. P. A component of the medicinal herb ephedra blocks activation in the classical and alternative pathways of complement. *Clin. Exp. Immunol.* 102: 582, 1995.

40. Sachdeva, R., Sivasankaran, S., Fishman, R. F., Zarich, S. W., and McPherson, C. A. Coronary thrombosis related to use of Xenadrine RFA. *Tex. Heart Inst. J.* 32: 74, 2005.
41. Kaye, A. D., Clarke, R. C., Sabar, R., et al. Herbal medicines: Current trends in anesthesiology practice—a hospital survey. *J. Clin. Anesth.* 12: 468, 2000.
42. Blanck, H. M., Khan, L. K., and Serdula, M. K. Use of nonprescription weight loss products: Results from a multistate survey. *J.A.M.A.* 286: 930, 2001.
43. Bent, S., Tiedt, T. N., Odden, M. C., and Shlipak, M. G. The relative safety of ephedra compared with other herbal products. *Ann. Intern. Med.* 138: 468, 2003.
44. Haller, C. A., and Benowitz, N. L. Adverse cardiovascular and central nervous system events associated with dietary supplements containing ephedra alkaloids. *N. Engl. J. Med.* 343: 1833, 2000.
45. U.S. Food and Drug Administration CfFSaAN. *Consumer Alert: FDA Plans Regulation Prohibiting Sale of Ephedra-Containing Dietary Supplements and Advises Consumers to Stop Using These Products.* United States Government, December 30, 2003.
46. Woolhouse, M., Silberstein, S. D., Pittler, M. H., Ernst, E., and Abebe, W. Migraine and tension headache: A complementary and alternative medicine approach. *Aust. Fam. Physician* 34: 647, 2005.
47. Diener, H. C., Pfaffenrath, V., Schnitker, J., Friede, M., and Henneicke-von Zepelin, H. H. Efficacy and safety of 6.25 mg t.i.d. feverfew CO₂-extract (MIG-99) in migraine prevention: A randomized, double-blind, multicentre, placebo-controlled study. *Cephalalgia* 25: 1031, 2005.
48. Cady, R. K., Schreiber, C. P., Beach, M. E., and Hart, C. C. Gelstat Migraine (sublingually administered feverfew and ginger compound) for acute treatment of migraine when administered during the mild pain phase. *Med. Sci. Monit.* 11: PI65, 2005.
49. Pittler, M. H., Ernst, E., and Abebe, W. Feverfew for preventing migraine. *Cochrane Database Syst. Rev.* 27: CD002286, 2004.
50. Abebe, W. Herbal medication: Potential for adverse interactions with analgesic drugs. *J. Clin. Pharm. Ther.* 27: 391, 2002.
51. Sumner, H., Salan, U., Knight, D. W., and Hoult, J. R. Inhibition of 5-lipoxygenase and cyclo-oxygenase in leukocytes by feverfew: Involvement of sesquiterpene lactones and other components. *Biochem. Pharmacol.* 43: 2313, 1992.
52. Capasso, F. The effect of an aqueous extract of *Tanacetum parthenium* L. on arachidonic acid metabolism by rat peritoneal leukocytes. *J. Pharm. Pharmacol.* 38: 71, 1986.
53. Ysrael, M. C., and Croft, K. D. Inhibition of leukotriene and platelet activating factor synthesis in leukocytes by the sesquiterpene lactone scandanolide. *Planta Med.* 56: 268, 1990.
54. Cheng, B., Hung, C. T., and Chiu, W. Herbal medicine and anaesthesia. *Hong Kong Med. J.* 8: 123, 2002.
55. Mashour, N. H., Lin, G. I., and Frishman, W. H. Herbal medicine for the treatment of cardiovascular disease: Clinical considerations. *Arch. Intern. Med.* 158: 2225, 1998.
56. Ackermann, R. T., Mulrow, C. D., Ramirez, G., Gardner, C. D., Morbidoni, L., and Lawrence, V. A. Garlic shows promise for improving some cardiovascular risk factors. *Arch. Intern. Med.* 161: 813, 2001.
57. Ali, M., Thomson, M., and Afzal, M. Garlic and onions: Their effect on eicosanoid metabolism and its clinical relevance. *Prostaglandins Leukot. Essent. Fatty Acids* 62: 55, 2000.
58. Thomson, M., Mustafa, T., and Ali, M. Thromboxane-B(2) levels in serum of rabbits receiving a single intravenous dose of aqueous extract of garlic and onion. *Prostaglandins Leukot. Essent. Fatty Acids* 63: 217, 2000.
59. Burnham, B. E. Garlic as a possible risk for postoperative bleeding. *Plast. Reconstr. Surg.* 95: 213, 1995.
60. Ang-Lee, M. K., Moss, J., and Yuan, C. S. Herbal medicines and perioperative care. *J.A.M.A.* 286: 208, 2001.
61. Bone, M. E., Wilkinson, D. J., Young, J. R., McNeil, J., and Charlton, S. Ginger root: A new antiemetic. The effect of ginger root on postoperative nausea and vomiting after major gynaecological surgery. *Anaesthesia* 45: 669, 1990.
62. Phillips, S., Ruggier, R., and Hutchinson, S. E. *Zingiber officinale* (ginger): An antiemetic for day case surgery. *Anaesthesia* 48: 715, 1993.
63. Norred, C. L., Zamudio, S., and Palmer, S. K. Use of complementary and alternative medicines by surgical patients. *A.A.N.A. J.* 68: 13, 2000.
64. Backon, J. Ginger: Inhibition of thromboxane synthetase and stimulation of prostacyclin: Relevance for medicine and psychiatry. *Med. Hypotheses* 20: 271, 1986.
65. Lumb, A. B. Effect of dried ginger on human platelet function. *Thromb. Haemost.* 71: 110, 1994.
66. Oken, B. S., Storzbach, D. M., and Kaye, J. A. The efficacy of *Ginkgo biloba* on cognitive function in Alzheimer disease. *Arch. Neurol.* 55: 1409, 1998.
67. Kleijnen, J., and Knipschild, P. *Ginkgo biloba.* *Lancet* 340: 1136, 1992.
68. Smith, P. F., Maclennan, K., and Darlington, C. L. The neuroprotective properties of the *Ginkgo biloba* leaf: A review of the possible relationship to platelet-activating factor (PAF). *J. Ethnopharmacol.* 50: 131, 1996.
69. Klepser, T. B., and Klepser, M. E. Unsafe and potentially safe herbal therapies. *Am. J. Health Syst. Pharm.* 56: 125, 1999.
70. Akiba, S., Kawachi, T., Oka, T., Hashizume, T., and Sato, T. Inhibitory effect of the leaf extract of *Ginkgo biloba* L. on oxidative stress-induced platelet aggregation. *Biochem. Mol. Biol. Int.* 46: 1243, 1998.
71. Rowin, J., and Lewis, S. L. Spontaneous bilateral subdural hematomas associated with chronic *Ginkgo biloba* ingestion. *Neurology* 46: 1775, 1996.
72. Vale, S. Subarachnoid haemorrhage associated with *Ginkgo biloba.* *Lancet* 352: 36, 1998.
73. Matthews, M. K., Jr. Association of *Ginkgo biloba* with intracerebral hemorrhage. *Neurology* 50: 1933, 1998.
74. Fessenden, J. M., Wittenborn, W., and Clarke, L. *Ginkgo biloba:* A case report of herbal medicine and bleeding postoperatively from a laparoscopic cholecystectomy. *Am. Surg.* 67: 33, 2001.
75. Rosenblatt, M., and Mindel, J. Spontaneous hyphema associated with ingestion of *Ginkgo biloba* extract. *N. Engl. J. Med.* 336: 1108, 1997.
76. White, H. L., Scates, P. W., and Cooper, B. R. Extracts of *Ginkgo biloba* leaves inhibit monoamine oxidase. *Life Sci.* 58: 1315, 1996.
77. Vuksan, V., Sievenpiper, J. L., Koo, V. Y., et al. American ginseng (*Panax quinquefolius* L) reduces postprandial glycemia in nondiabetic subjects and subjects with type 2 diabetes mellitus. *Arch. Intern. Med.* 160: 1009, 2000.
78. Kuo, S. C., Teng, C. M., Lee, J. C., Ko, F. N., Chen, S. C., and Wu, T. S. Antiplatelet components in *Panax ginseng.* *Planta Med.* 56: 164, 1990.
79. Ryu, S. J., and Chien, Y. Y. Ginseng-associated cerebral arteritis. *Neurology* 45: 829, 1995.
80. Janetzky, K., and Morreale, A. P. Probable interaction between warfarin and ginseng. *Am. J. Health Syst. Pharm.* 54: 692, 1997.

81. Jung, K. Y., Kim, D. S., Oh, S. R., et al. Platelet activating factor antagonist activity of ginsenosides. *Biol. Pharm. Bull.* 21: 79, 1998.
82. Visalyaputra, S., Petchpaisit, N., Somcharoen, K., and Choavaratana, R. The efficacy of ginger root in the prevention of postoperative nausea and vomiting after outpatient gynaecological laparoscopy. *Anaesthesia* 53: 506, 1998.
83. Norred, C. L., and Finlayson, C. A. Hemorrhage after the preoperative use of complementary and alternative medicines. *A.A.N.O. J.* 68: 217, 2000.
84. McRae, S. Elevated serum digoxin levels in a patient taking digoxin and Siberian ginseng. *C.M.A.J.* 155: 293, 1996.
85. Abadie, E., Ethgen, D., Avouac, B., et al. Recommendations for the use of new methods to assess the efficacy of disease-modifying drugs in the treatment of osteoarthritis. *Osteoarthritis. Cartil.* 12: 263, 2004.
86. Pavelka, K., Gatterova, J., Olejarova, M., Machacek, S., Giacovelli, G., and Rovati, L. C. Glucosamine sulfate use and delay of progression of knee osteoarthritis: A 3-year, randomized, placebo-controlled, double-blind study. *Arch. Intern. Med.* 162: 2113, 2002.
87. Stupay, S., and Sivertsen, L. Herbal and nutritional supplement use in the elderly. *Nurse Pract.* 25: 56, 2000.
88. Joshi, S. S., Kuszynski, C. A., and Bagchi, D. The cellular and molecular basis of health benefits of grape seed proanthocyanidin extract. *Curr. Pharm. Biotechnol.* 2: 187, 2001.
89. Bagchi, D., Bagchi, M., Stohs, S. J., et al. Free radicals and grape seed proanthocyanidin extract: Importance in human health and disease prevention. *Toxicology* 148: 187, 2000.
90. U.S. Food and Drug Administration CFFSaAN. *Consumer Advisory: Kava-Containing Dietary Supplements May be Associated With Severe Liver Injury.* United States Government, March 25, 2002.
91. Gleitz, J., Beile, A., Wilkens, P., Ameri, A., and Peters, T. Antithrombotic action of the kava pyrone (+)-kavain prepared from Piper methysticum on human platelets. *Planta Med.* 63: 27, 1997.
92. Almeida, J. C., and Grimsley, E. W. Coma from the health food store: Interaction between kava and alprazolam. *Ann. Intern. Med.* 125: 940, 1996.
93. Hu, Z., Yang, X., Ho, P. C., et al. Herb-drug interactions: A literature review. *Drugs* 65: 1239, 2005.
94. Izzo, A. A., and Ernst, E. Interactions between herbal medicines and prescribed drugs: A systematic review. *Drugs* 61: 2163, 2001.
95. Famularo, G., Corsi, F. M., and Giacanelli, M. Iatrogenic worsening of hypokalemia and neuromuscular paralysis associated with the use of glucose solutions for potassium replacement in a young woman with licorice intoxication and furosemide abuse. *Acad. Emerg. Med.* 6: 960, 1999.
96. Kromhout, D., Bosschieter, E. B., and de Lezenne Coulander, C. The inverse relation between fish consumption and 20-year mortality from coronary heart disease. *N. Engl. J. Med.* 312: 1205, 1985.
97. Iso, H., Rexrode, K. M., Stampfer, M. J., et al. Intake of fish and omega-3 fatty acids and risk of stroke in women. *J.A.M.A.* 285: 304, 2001.
98. Archer, S. L., Green, D., Chamberlain, M., Dyer, A. R., and Liu, K. Association of dietary fish and n-3 fatty acid intake with hemostatic factors in the coronary artery risk development in young adults (CARDIA) study. *Arterioscler. Thromb. Vasc. Biol.* 18: 1119, 1998.
99. Weksler, B. B. Omega 3 fatty acids have multiple antithrombotic effects. *World Rev. Nutr. Diet.* 76: 47, 1994.
100. Knapp, H. R. Dietary fatty acids in human thrombosis and hemostasis. *Am. J. Clin. Nutr.* 65: 1687S, 1997.
101. Kromann, N., and Green, A. Epidemiological studies in the Upernavik district, Greenland: Incidence of some chronic diseases 1950–1974. *Acta Med. Scand.* 208: 401, 1980.
102. Stacpoole, P. W., Alig, J., Ammon, L., and Crockett, S. E. Dose-response effects of dietary marine oil on carbohydrate and lipid metabolism in normal subjects and patients with hypertriglyceridemia. *Metabolism* 38: 946, 1989.
103. Kris-Etherton, P. M., Harris, W. S., and Appel, L. J. Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease. *Circulation* 106: 2747, 2002.
104. Cheema, P., El-Mefty, O., and Jazieh, A. R. Intraoperative haemorrhage associated with the use of extract of saw palmetto herb: A case report and review of literature. *J. Intern. Med.* 250: 167, 2001.
105. Muller, W. E., Singer, A., Wonnemann, M., Hafner, U., Rolli, M., and Schafer, C. Hyperforin represents the neurotransmitter reuptake inhibiting constituent of hypericum extract. *Pharmacopsychiatry* 31 Suppl. 1: 16, 1998.
106. Woelk, H. Comparison of St. John's wort and imipramine for treating depression: Randomised controlled trial. *B.M.J.* 321: 536, 2000.
107. Irefin, S., and Sprung, J. A possible cause of cardiovascular collapse during anesthesia: Long-term use of St. John's wort. *J. Clin. Anesth.* 12: 498, 2000.
108. Roby, C. A., Anderson, G. D., Kantor, E., Dryer, D. A., and Burstein, A. H. St. John's wort: Effect on CYP3A4 activity. *Clin. Pharmacol. Ther.* 67: 451, 2000.
109. Nebel, A., Schneider, B. J., Baker, R. K., and Kroll, D. J. Potential metabolic interaction between St. John's wort and theophylline. *Ann. Pharmacother.* 33: 502, 1999.
110. Barone, G. W., Gurley, B. J., Ketel, B. L., Lightfoot, M. L., and Abul-Ezz, S. R. Drug interaction between St. John's wort and cyclosporine. *Ann. Pharmacother.* 34: 1013, 2000.
111. Johne, A., Brockmoller, J., Bauer, S., Maurer, A., Langheinrich, M., and Roots, I. Pharmacokinetic interaction of digoxin with an herbal extract from St. John's wort (*Hypericum perforatum*). *Clin. Pharmacol. Ther.* 66: 338, 1999.
112. Brockmoller, J., Reum, T., Bauer, S., Kerb, R., Hubner, W. D., and Roots, I. Hypericin and pseudohypericin: Pharmacokinetics and effects on photosensitivity in humans. *Pharmacopsychiatry* 30 Suppl. 2: 94, 1997.
113. Wagner, J., Wagner, M. L., and Hening, W. A. Beyond benzodiazepines: Alternative pharmacologic agents for the treatment of insomnia. *Ann. Pharmacother.* 32: 680, 1998.
114. Caldwell, S. H., Feeley, J. W., Wieboldt, T. F., Featherston, P. L., and Dickson, R. C. Acute hepatitis with use of over-the-counter herbal remedies. *Va. Med. Q.* 121: 31, 1994.
115. Garges, H. P., Varia, I., and Doraiswamy, P. M. Cardiac complications and delirium associated with valerian root withdrawal. *J.A.M.A.* 280: 1566, 1998.
116. Kaufman, D. W., Kelly, J. P., Rosenberg, L., Anderson, T. E., and Mitchell, A. A. Recent patterns of medication use in the ambulatory adult population of the United States: The Slone survey. *J.A.M.A.* 287: 337, 2002.
117. Williamson, E. M. Drug interactions between herbal and prescription medicines. *Drug Saf.* 26: 1075, 2003.
118. Russell, R. M. The vitamin A spectrum: From deficiency to toxicity. *Am. J. Clin. Nutr.* 71: 878, 2000.
119. Phillips, J. D., Kim, C. S., Fonkalsrud, E. W., Zeng, H., and Dindar, H. Effects of chronic corticosteroids and vitamin A on the healing of intestinal anastomoses. *Am. J. Surg.* 163: 71, 1992.

120. Talas D. U. Nayci, A., Atis, S., et al. The effects of corticosteroids and vitamin A on the healing of tracheal anastomoses. *Int. J. Pediatr. Otorhinolaryngol.* 67: 109, 2003.
121. Winsey, K., Simon, R. J., Levenson, S. M., Seifter, E., and Demetriou, A. A. Effect of supplemental vitamin A on colon anastomotic healing in rats given preoperative irradiation. *Am. J. Surg.* 153: 153, 1987.
122. Haws, M., Brown, R. E., Suchy, H., and Roth, A. Vitamin A-soaked gelfoam sponges and wound healing in steroid-treated animals. *Ann. Plast. Surg.* 32: 418, 1994.
123. Eussen, S. J., de Groot, L. C., Clarke, R., et al. Oral cyanocobalamin supplementation in older people with vitamin B12 deficiency: A dose-finding trial. *Arch. Intern. Med.* 165: 1167, 2005.
124. Oh, R., and Brown, D. L. Vitamin B12 deficiency. *Am. Fam. Physician* 67: 979, 2003.
125. Jansen, T., Romiti, R., Kreuter, A., and Altmeyer, P. Rosacea fulminans triggered by high-dose vitamins B6 and B12. *J. Eur. Acad. Dermatol. Venerol.* 15: 484, 2001.
126. Diaz, D. E., Tuesta, A. M., Ribo, M. D., et al. Low levels of vitamin B12 and venous thromboembolic disease in elderly men. *J. Intern. Med.* 258: 244, 2005.
127. Giusti, B., Marcucci, R., Lapini, I., et al. Role of hyperhomocysteinemia in aortic disease. *Cell. Mol. Biol. (Noisy-le-grand)* 50: 945, 2004.
128. Arcaro, G., Fava, C., Dagradi, R., et al. Acute hyperhomocysteinemia induces a reduction in arterial distensibility and compliance. *J. Hypertens.* 22: 775, 2004.
129. Choy, P. C., Mymin, D., Zhu, Q., and Dakshinamurti, K. O. K. Atherosclerosis risk factors: The possible role of homocysteine. *Mol. Cell. Biochem.* 207: 143, 2000.
130. Demuth, K., Drunat, S., Girerd, X., et al. Homocysteine is the only plasma thiol associated with carotid artery remodeling. *Atherosclerosis* 165: 167, 2002.
131. Costea, A., and Bhat, G. Hyperhomocysteinemia and deep vein thrombosis in orthotopic heart transplantation: A case report. *Am. J. Hematol.* 77: 161, 2004.
132. Eichinger, S. Homocysteine, vitamin B6 and the risk of recurrent venous thromboembolism. *Pathophysiol. Haemost. Thromb.* 33: 342, 2003.
133. Yang, F., Tan, H. M., and Wang, H. Hyperhomocysteinemia and atherosclerosis. *Sheng Li Xue Bao* 57: 103, 2005.
134. Anderson, T. W. Large-scale trials of vitamin C. *Ann. N. Y. Acad. Sci.* 258: 498, 1975.
135. Hemila, H. Vitamin C intake and susceptibility to the common cold. *Br. J. Nutr.* 77: 59, 1997.
136. Moertel, C. G., Fleming, T. R., Creagan, E. T., Rubin, J., O'Connell, M. J., and Ames, M. M. High-dose vitamin C versus placebo in the treatment of patients with advanced cancer who have had no prior chemotherapy: A randomized double-blind comparison. *N. Engl. J. Med.* 312: 137, 1985.
137. Institute of Medicine FaNb. *Dietary Reference Intakes: Vitamin C, Vitamin E, Selenium, and Carotenoids.* Washington, D.C.: National Academy Press, 2000.
138. Rees, D. C., Kelsey, H., and Richards, J. D. Acute haemolysis induced by high dose ascorbic acid in glucose-6-phosphate dehydrogenase deficiency. *B.M.J.* 306: 841, 1993.
139. Sestili, M. A. Possible adverse health effects of vitamin C and ascorbic acid. *Semin. Oncol.* 10: 299, 1983.
140. Massey, P. B. Dietary supplements. *Med. Clin. North Am.* 86: 127, 2002.
141. Stampfer, M. J., Hennekens, C. H., Manson, J. E., Colditz, G. A., Rosner, B., and Willett, W. C. Vitamin E consumption and the risk of coronary disease in women. *N. Engl. J. Med.* 328: 1444, 1993.
142. Miller, E. R., III, Pastor-Barriuso, R., Dalal, D., Riemersma, R. A., Appel, L. J., and Guallar, E. Meta-analysis: High-dosage vitamin E supplementation may increase all-cause mortality. *Ann. Intern. Med.* 142: 37, 2005.
143. Bistrrian, B. By the way, doctor. I take vitamin E pills, but I've heard they can cause bleeding. Is this anything to worry about? *Harv. Health Lett.* 28: 8, 2002.
144. Booth, S. L., Golly, I., Sackeck, J. M., et al. Effect of vitamin E supplementation on vitamin K status in adults with normal coagulation status. *Am. J. Clin. Nutr.* 80: 143, 2004.
145. Dowd, P., and Zheng, Z. B. On the mechanism of the anticlotting action of vitamin E quinone. *Proc. Natl. Acad. Sci. U.S.A.* 92: 8171, 1995.
146. Gonzalez-Correa, J. A., Arrebola, M. M., Guerrero, A., et al. Influence of vitamin E on the antiplatelet effect of acetylsalicylic acid in human blood. *Platelets* 16: 171, 2005.
147. Heck, A. M., DeWitt, B. A., and Lukes, A. L. Potential interactions between alternative therapies and warfarin. *Am. J. Health Syst. Pharm.* 57: 1221, 2000.
148. Corrigan, J. J., Jr. The effect of vitamin E on warfarin-induced vitamin K deficiency. *Ann. N. Y. Acad. Sci.* 393: 361, 1982.
149. Kim, J. M., and White, R. H. Effect of vitamin E on the anticoagulant response to warfarin. *Am. J. Cardiol.* 77: 545, 1996.
150. Bent, S., and Ko, R. Commonly used herbal medicines in the United States: A review. *Am. J. Med.* 116: 478, 2004.
151. Labels CoDS. *Report of the Commission on Dietary Supplement Labels, Report of the President, Congress, and the Secretary of the Department of Health and Human Services.* Washington, D.C.: U.S. Government Printing Office, 1997.