AMERICAN ACADEMY OF OPHTHALMOLOGY
The Eye M.D. Association

COMPLEMENTARY THERAPY ASSESSMENT

NUTRITIONAL SUPPLEMENTS: PERIOPERATIVE IMPLICATIONS FOR EYE SURGERY

November 2003

SUMMARY

The purpose of this complementary assessment is:

- to assist physicians and their patients with potential prescribed medication-nutritional supplement interactions especially in the perioperative period
- to answer questions patients may pose about the ophthalmic use of herbals and potential benefits and side effects
- to further our understanding of the impact that nutritional supplement use has on patient health and well-being

This assessment is not meant to cover every potential side effect that a nutritional supplement may cause but the ones of most importance to the physician-patient team. This assessment does not contain information on herbs used in other healing traditions, such as in Chinese medicine. Although this information will be updated periodically, it may not be complete on a specific supplement or problem. Health-related information changes frequently and therefore information contained in this assessment may be outdated, incomplete, or incorrect. Very few randomized controlled clinical trials exist for the use of nutritional supplements. Much of the material in this assessment is drawn from studies of small series of patients and anecdotal information. Much of the material in print merits further scientific validation and verification. The Food and Drug Administration has not evaluated statements made about products.

The material in this complementary therapy assessment has not been reviewed or approved by the Board of Trustees of the American Academy of Ophthalmology and does not in any way constitute a guideline or policy of the American Academy of Ophthalmology. This material has been developed by the American Academy of Ophthalmology to inform its members.

The assessment contains the following:

- Preoperative screening questionnaire for nutritional supplement use
- Table 1 for easy referral for information about nutritional supplements
- Reference review of nutritional supplements for additional information
- Reporting form for perioperative events when the patient has used nutritional supplements
- Poster for office use of nutritional supplements and drug interactions
- Web site links for further information on the topic

INTRODUCTION TO THE TOPIC

Herbal medicine use is becoming more and more common. In 1997, about 12% of the United States population used supplements;[1, 2] in 2002, 32% of patients undergoing ambulatory surgery used supplements.[3] As early as 1998, estimates show that at least one-half of adults in the United States used dietary supplements and up to one-third may use herbal medicinals.[4-6] In one study of almost 1,000 patients undergoing ambulatory surgery, 90% were using vitamins; 43% used garlic supplements, 32% used ginkgo biloba extract, 30% used St. John's wort, and 18% used Ma Huang, 12% used Echinacea.[3] The use of supplements, at least in the presurgical group, appears more likely in patients who are also taking traditional over-the-counter medications.[7] The use of alternative medicine, home remedies, and dietary supplements also appears more likely among some ethnic groups such as Asians and Hispanics.[8] However, failure to disclose herbal use to physicians occurs in 60% to 80% of patients[9] due to:

- Failure to consider them as medication; "natural means safe"
- Fear that physicians are not supportive of unconventional medication
- Lack of awareness of potential risks associated with alternative medication use[3]
- Easy access; cuts out the need to see a physician and may prevent the need to discuss embarrassing problems, e.g., sexual dysfunction.[10]

CONCLUSIONS

The effects of herbals are diverse and can be adverse. Their use is disseminated throughout the population and merits observation. Yet patients do not readily offer information about their supplement use to their physicians. If a surgical procedure is contemplated or untoward event occurs, it is important for the physician to ask the patient about any use of complementary or alternative medications. It is also important to remember that the agents covered in this assessment are some of the more popular agents sold and used in the United States and that patients use many other healing traditions.

BENEFITS & RISKS

The benefits to some patients involve risks to others and will be considered together; this will be done initially, in general, and then for each herbal in the Report section.

Anticoagulant effects – **4 G's-3F's, L&C**: **garlic, ginger, ginseng, ginkgo, and also feverfew, fish oils, fenugreek**, **licorice and coenzyme Q10.** For those and other effects see Table 1. Vitamin E, glucosamine, and evening primrose oil have anticoagulant effects.

Cardiovascular effects – **Ephedra** is a direct sympathomimetic; **licorice** & **cascara** increase cardiac glycosides; **lily-of-the-valley** is a cardioactive glycoside. Ginseng, gamma hydroxybutyrate (GHB), gamma butyrolactone or butyrolactone gamma (GBL) St John's wort (secondary to effects on digoxin levels) and triiodothyroacetic acid have cardiovascular effects.

Analgesia & herbals – The hepatoxicity of acetaminophen is increased with concomitant echinacea and kava. Opioid analgesics will be increased with valerian, kava, and chamomile; they may be decreased by ginseng. Potential for prolongation of anesthesia with valerian and kava.

Direct ocular effect – **Bilberry**, **St. John's wort**, and **licorice** (details in text).

Other effects – **Borage leaf, coltsfoot, comfrey, life root** contain pyrrolizidine alkaloids, linked to hepatic cancer in animals. **Chaparral** and **germander** cause jaundice, pruritus, fatigue, cholestasis, and hepatic necrosis in humans. Renal insufficiency or hepatotoxicity is possible with **licorice** (renal), **creatine** (renal), **echinacea** (hepatic), and **kava** (hepatic). Abnormal thyroid function is possible with shark cartilage, vitamin E, soy proteins, and triiodothyroacetic acid.

Herbal-drug interaction through Cytochrome P450(3A4,2C9,2D6) or P-glycoprotein metabolism- Individual susceptibility to this factor exists in those people who are poor absorbers of drugs; in the US, this is thought to represent up to 7% of Caucasian populations and up to 20% of the Asian population.[11] Drugs that rely on the intestinal wall for absorption are most affected especially if they have a narrow therapeutic window. Cytochrome P450 3A4 is active in the metabolism of calcium channel blockers (especially felodipine), benzodiazepines, HIV protease inhibitors, HMG-CoA-reductase inhibitors, cyclosporine, and nonsedating antihistamines, and decreases digoxin levels in healthy volunteers secondary to P4SO3A4 induction.[12-14] Cytochrome 2C helps metabolize anti-convulsant medications. P-glycoproteins are important in the elimination of medications.[11, 13]

Grapefruit juice and **echinacea** are cytochrome enzyme inhibitors; **ginkgo, kava, garlic, goldenseal** and **St. John's wort** are specific herbals implicated as cytochrome P450 inducers.

REPORT

DEFINITION OF THE PROBLEM

Herbal medicine use is becoming more and more common. In 1997, about 12% of the United States population used supplements;[1, 2] in 2002, 32% of patients undergoing ambulatory surgery used supplements.[3] As early as 1998, estimates show that at least one-half of adults in the United States used dietary supplements and up to one-third may use herbal medicinals.[4-6] In one study of almost 1,000 patients undergoing ambulatory surgery, 90% were using vitamins; 43% used garlic supplements, 32% used ginkgo biloba extract, 30% used St. John's wort, 18% used Ma Huang, and 12% used echinacea.[3] The use of supplements, at least in the presurgical group, appears more likely in patients who are also taking traditional over-the-counter medications.[7] The use of oriental medicine, home remedies, and dietary supplements also appears more likely among some ethnic groups such as Asians and Hispanics.[8] However, failure to disclose herbal use to physicians occurs in 60% to 80% of patients[9] due to:

- Failure to consider them as medication; "natural means safe"
- Fear that physicians are not supportive of unconventional medication
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- Easy access; cuts out the need to see a physician and may prevent the need to discuss embarrassing problems, e.g., sexual dysfunction.[10]

FDA STATUS/LEGAL STATUS

According to the NIH Office of Dietary Supplements,[15] the Dietary Supplement Health and Education Act of 1994 defines dietary supplements as a product (other than tobacco) intended to supplement the diet that bears or contains one or more of the following dietary ingredients: a vitamin, mineral, amino acid, herb, or other botanical; or a dietary substance for use to supplement the diet by increasing the total dietary intake; or a concentrate, metabolite, constituent, extract, or combination of any ingredient described above. Any of these must be intended for ingestion in the form of a capsule, powder, tablet, softgel, liquid, or gelcap, and must not be represented as a conventional food or as a sole item of a meal or the diet. Other forms that these products may present in are fresh decoctions (chopped); whole herbs steeped as teas; tinctures (fresh or dried herbs preserved in alcohol); vinegar extracts; syrups; glycerites (in vegetable glycerin); miels (in honey); freeze-dried or powders (which may come in bulk, tablet, troche, capsule, or concentrate forms); suppositories, creams, liniments, oils, or compresses.[16]

Dietary supplements are widely available through many commercial sources including health food stores, grocery stores, and pharmacies and by mail and on the Internet. Historically in the United States, the most prevalent type of dietary supplement was a multivitamin/mineral tablet or capsule that was available in pharmacies by prescription or "over the counter." Supplements containing strictly herbal preparations were less widely available. Currently in the United States, a wide array of supplement products are available, including vitamins, minerals, and other nutrients; botanical supplements; and ingredients and extracts of animal and plant origin, but producers of supplements are not allowed to attribute any potential health benefit to their products.

The Dietary Supplement Health and Education Act of 1994 limits the authority of the Food and Drug Administration (FDA) over these products since they are not classified as drugs. The FDA requirement for pre-market review of dietary supplements is less than that over other products it regulates, such as drugs and many additives used in conventional foods. The FDA oversees safety, manufacturing, and product information such as claims, in a product's labeling, package inserts, and accompanying literature. The Federal Trade Commission, which oversees advertising, has issued advertising guidelines, and has taken a number of enforcement actions against companies whose

advertisements contained false and misleading information. As of February 2002, the United States Pharmacopeia (USP) is acting as an oversight mechanism for ensuring safe manufacturing practices. As of 2003, the FDA has proposed a plan for "Current Good Manufacturing Practices, which is designed to protect the public from adulterated products, provide consistent industry-wide requirements, and to ensure quality, not safety or efficacy of dietary supplements'.[17]

BENEFITS AND RISKS OF SPECIFIC HERBALS

Bilberry (*Vaccinium myrtillus*)

Active Ingredient: Anthocyanidins have a short half-life.

Mechanism & Benefits: Bilberry stimulates the regeneration of rhodopsin, has a positive effect on capillary fragility, and lowers blood sugar. In one study of young males, with generally good vision, no benefit was seen to high dose bilberry on night vision or night contrast sensitivity.[19]

Potential Side Effects & Precautions: none known to date

Black cohosh may increase the effect of antihypertensives and may also cause visual disturbances (type not specified in this source).[20]

Cascara may potentiate the cardiac glycosides and antiarrhythmic drugs because of potassium deficiency brought on by use of this substance.

Chamomile (*Matricaria recutita*)

Active Ingredient: chamazulene, apigenin, bisabolol

Mechanism & Benefits: It inhibits CYP3A4, thus, it decreases metabolism and increases serum concentration of calcium channel drugs, cisapride, lovastatin, and simvastatin.

Potential Side Effects & Precautions: It appears to have an additive effect when combined with sedative and natural products such as kava, lemon balm and valerian.[21] It is possible that use of chamomile in combination with these herbs might prolong the effects of anesthesia.

Coenzyme Q_{10} (CoQ_{10})

Active ingredient: same; the half-life is 34 hours due to enterohepatic recirculation.

Mechanism & Benefits: CoQ_{10} is a provitamin synthesized by the body to function in mitochondrial transport for the synthesis of ATP and also as a membrane stabilizer by reducing free radicals; thus, it is a potent antioxidant. Its structure is similar to vitamin K. It has accordingly been used in CHF, angina, and hypertension. Parkinson disease (PD) patients have low levels of CoQ_{10} in their platelet mitochondria and lower serum levels of CoQ_{10}, and CoQ_{10} appears to increase the functional neurological ability in PD patients.[22]

Potential Side Effects & Precautions: It may diminish warfarin anticoagulation and decrease the international normalized ratio (INR). It may also decrease insulin requirements by its effect on adenosine triphosphatase (ATP).[23] Vague photophobia and headache has occasionally been cited. Thrombocytopenia is also known to occur with CoQ_{10} use.[24]

Echinacea (*Echinacea purpurea, pallida, and augustiflora***)**

Active ingredient: Product is often standardized to total phenols but active ingredient is unclear.

Mechanism & Benefits: It is commonly used as acute prophylaxis for viral, bacterial, and fungal treatments (immunostimulatory effect short-term). Echinacea inhibits CYP3A4.[21]

Potential Side Effects & Precautions: Due to cytochrome inhibition, concurrent use with alprazolam, calcium channel blockers, and protease inhibitors increases drug levels.[21] Echinacea use by patients who are on immunosuppressive agents may acutely offset the immunosuppressive response.[12] However, long-term use (more than 8 weeks) may cause immunosuppression and increased infections and allergic reactions are potentiated. There is potential hepatotoxicity because it contains pyrrolizidine alkaloids but these are not thought to be hepatotoxic. It may potentiate barbiturate toxicity. Echinacea decreases the clearance of tolbutamide and caffeine.[12, 25-27]

Ephedra or **Ma Huang** (*Ephedra sinensis*)

Active Ingredient: ephedrine and pseudoephedrine

Mechanism & Benefits: It does cause weight loss, increased energy, and ameliorates asthma.[28] It has a nonselective adrenergic agonist activity.

Potential Side Effects & Precautions: Samenuk et al[29] noted a temporal link between Ma Huang and 11 sudden deaths, 16 cerebrovascular accidents, and 10 myocardial infarctions. Of the 11 sudden deaths, one patient had a normal heart at autopsy. In 36 of these 37 patients the dosage was within the manufacturers' recommended dosage. There were also 926 adverse effects including hallucinations.[29] Other adverse events have been reported including cerebral bleeds, persistent psychosis, panic attacks, palpitations, headaches, chest pain, arrhythmias, memory loss, sudden hearing loss, hepatotoxicity, dysuria, urinary retention, uterine contractions, and dyspnea.[30-32] Ephedra causes dose-dependent increases in heart rate and blood pressure and may sensitize to intraoperative ventricular arrhythmia when halothane anesthesia is used.[29] Ephedra and monoamine oxidase (MAO) inhibitors can be associated with hyperpyrexia, hypertension, and coma.[3, 29, 33] Ephedra and guanethidine can be associated with enhanced sympathomimetic effects; ephedra and oxytocin can be associated with hypertension; ephedra and phenothiazine can be associated with tachycardia.[34] Hypertensive crisis can be associated with concurrent use of ephedra and tricyclics; concurrent use with xanthines can be associated with increased central nervous system stimulation.[34] Ephedra has also been linked to an increased risk of kidney stones, psychoses, and mood disorders.[33]

Evening primrose & Borage seed oil

Active Ingredient: The essential fatty acids contain gamma-linolenic acid.

Mechanism & Benefits: Essential fatty acids are rich in prostaglandin E_1, an indirect anti-inflammatory, and are being evaluated for rheumatoid arthritis and keratoconjunctivitis sicca.

Potential Side Effects & Precautions: Evening primrose oil may cause lack of seizure control when combined with phenytoin.[35, 36] Only borage leaf oil contains toxic pyrrolizidine alkaloids.[37] Evening primrose oil may increase the anticoagulant effect of drugs such as warfarin.[38]

Fenugreek

Active Ingredient: hydroxy isoleucine

Mechanism & Benefits: It stimulates the pancreas to release insulin (therefore causing a hypoglycemic effect) and it also interferes with iron metabolism. It can lower LDL cholesterol.

Potential Side Effects & Precautions: Fenugreek may alter thyroid hormone balance.

Feverfew *(Tanacetum parthenium)*

Active Ingredient: unclear

Mechanism and Benefits: It is a spasmolytic causing decreased reactivity of smooth muscles (cerebral blood vessels); there is decreased production of serotonin by white blood cells and platelets as well as decreased production of leukotrienes by white blood cells. It is generally used to decrease headaches.

Potential Side Effects and Precautions: Adverse interactions may occur from feverfew in those allergic to ragweed. Nonsteroidal anti-inflammatory agents decrease herbal effect. There may be an increased hemodynamic instability.[3] Patients with coagulation disorders or on anticoagulants or antithrombolytics may experience adverse interactions. The mechanism of action on platelets is thought to be inhibition of serotonin release from aggregating platelets, as well as the possible inhibition of cell phospholipases, which prohibit release of arachadonic acid, a part of the inflammatory response.[39, 40]

Garlic *(Allium sativum*)

Active Ingredient: unclear

Mechanism & Benefits: Garlic can be an anticoagulant especially when taken with aspirin, other antiplatelet agents, warfarin, or indomethacin. Garlic can double a previously stable INR in a patient being treated with warfarin.[37, 41] Garlic inhibits epinephrine-induced platelet aggregation in a dose-dependent fashion that may be irreversible and in vitro inhibits calcium uptake by platelets. Garlic extract diminishes platelet adhesion to fibrinogen by 30% in subjects compared to controls; hence it does not primarily affect prothrombin time but only bleeding time.[25, 37, 42]

Potential Side Effects & Precautions: There are several anecdotal reports of moderately severe bleeding in patients who ingest heavy, chronic garlic. One elderly patient who was a heavy garlic user developed a spontaneous epidural hematoma. Elevated INR and prothrombin times can occur in patients that had been previously stabilized on warfarin.[42] Use of garlic for several days can also decrease protease inhibitor serum levels (through cytochrome CYP450 pathway interaction) in patients with HIV[43]and/or P-glycoprotein or production of a sidinavir metabolite.

Ginger (*Zingiber officinale*)

Active ingredient: unclear

Mechanism & Benefits: In anecdotal reports, ginger may have an additive effect on bleeding time. Although a dose-dependent reduction in platelet thromboxane has been suspected from in vitro studies, this has not been confirmed in clinical studies.[25, 42]
Ginger may also reduce vertigo and is most frequently used as an antiemetic.[25]

Potential Side Effects & Precautions: Ginger may increase the risk of intraoperative hemodynamic instability.[3]

Ginkgo biloba

Active ingredients: Primary substances appear to be Ginkgo biloba extract (GBE), ginkgo flavonoid (ginkgo-flavone glycosides-kaempferol, quercetin, isorhamnetin, etc.) and/or terpenoids (ginkgolides A,B,C,J, and M and bilobalide); the overall half-life is 3 is 10 hours.[44]

Mechanism & Benefits: Ginkgo flavonoids inhibit platelet aggregation and have antioxidant action, preventing membrane damage by free radicals; ginkgo terpenoids may also inhibit platelet-activating factor, produce central peripheral vasodilatation and affect prostaglandin metabolism.[45]

Ginkgo biloba has been suggested for use in memory loss, cerebrovascular disease, and dementia, as well as poor attention span, tinnitus, fatigue, macular degeneration, and glaucoma.[26] It may be the modulatory effect of ginkgo on the human cholinergic system that accounts for its effect in Alzheimer's disease; it appears not to have any effect on older subjects who do not have a cognitive abnormality.[46, 47] Flavonoids exhibit GABAergic activity (GABA=gamma-aminobutyric acid) and are partial agonists at benzodiazepine-binding sites; they also induce cytochrome P450 3A4.[41] Ginkgo extract has a high affinity for glandular and neuronal tissues, and the eye.[44] The use in glaucoma may relate to an increase in blood flow, decrease in vasospasm, serum viscosity, and a neuroprotective effect with a decrease in apoptosis.[48] Platelet activating factor receptors in the retina in animal models can respond to ginkgo and limit chloroquine-induced electroretinogram changes, ischemia-reperfusion injury, and diabetic retinal damage.[48] In animal studies, ginkgo appears to improve free-radical vitreoretinopathy in inflammatory and toxic (vincristine and chloroquine) ocular disease; it also appears to decrease and delay cellular proliferation and vitreous membranes.[45]

Potential Side Effects & Precautions: While there have not been clearly associated problems in clinical trials, there have been several cases of seizure and spontaneous intracranial bleeding (subdural hematoma, subarachnoid hemorrhage).[49-52] There are several reported cases of a seizure temporally linked with ginkgo in patients who had been previously been seizure free or controlled possibly due to a reduction in the effect of some seizure medications from ginkgo. Electroencephalographic changes in theta activity have been linked to contamination with ginkgo seeds.[53, 54] The seeds contain 4'-O-methylpyridoxine which is a neurotoxin; there are only minute amounts in ginkgo leaf.[37] It may, as well, decrease the effectiveness of anticonvulsants (e.g., carbamazepine, phenytoin, and phenobarbital) due to flavonoids acting as partial agonists at benzodiazepine-binding sites. Ginkgo flavonoids may have increased GABA activity, which can be potentiated by trazodone, and increased sedation may occur.[41]

Concurrent ginkgo biloba extract use with nonsteroidal anti-inflammatory drugs, heparin, or coumadin may be associated with an increased risk of bleeding.[55] A prolonged bleeding time, thrombin time, and partial thromboplastin time have been demonstrated in animal studies and isolated human subjects.[42, 45] There has also been spontaneous hyphema from iris vessels and postoperative bleeding following abdominal laparoscopy.[44, 56] Alkyl phenol contamination from ginkgo seed may cause cross-over allergy in patients sensitized to poison ivy, sumac, and oak as well as mango and cashew.[45] Myoglobinuria has been reported with the combined use of ginkgo, guarana and kava.[57] Mild gastrointestinal upset can also occur including diarrhea, nausea and vomiting.[55]

Ginseng extract *(Panax ginseng, Panax quinquefolius) (Eleutherococcus senticosus, also known as Siberian ginseng, belongs to a different genus than Panax ginseng; most ginseng for sale is Panax ginseng.)*

Active Ingredient: Ginsenosides and panaxans have a half-life between 1 to 8 hours but platelet inhibition may be irreversible.[58] Other active ingredients are triterpene, saponins, aglycone-protoparaxadiol, aglycone (including ginsenoside), aglycone oleanolic acid, water-soluble polysaccharides, and polynes.

Mechanism & Benefits: Ginseng lowers postprandial blood sugar and hemoglobin A_{1c} in diabetic patients and nondiabetic patients by accelerating hepatic lipogenesis as well as glycogen storage.[21, 26] This may be a problem especially in patients fasting for surgery as they may become hypoglycemic.[26] Ginseng inhibits platelet aggregation in in vitro studies. Ginseng, in an isolated report, decreased established international normalized ratios (INR) of patients on coumadin.[42] Another case study suggests that there may be severe bleeding diathesis in the perioperative period.[59] It also interacts with phenelzine sulfate, a monoamine oxidase inhibitor, probably by inhibiting cyclic adenosine monophosphate.[12, 41] Korean ginseng improved erectile dysfunction, sexual desire, and satisfaction with intercourse.[60]

Potential Side Effects & Precautions: Ginseng may interfere with antihypertensive medications. Concurrent ginseng use with other stimulants may cause tachycardia or hypertension and it may cause falsely elevated digoxin levels. Ginseng with warfarin, heparin, aspirin, or nonsteroidal anti-inflammatory agents may be associated with a possible increase in bleeding.[25] Adverse effects are few and include diarrhea, headache, vaginal bleeding, and Stevens-Johnson syndrome.[26]

Goldenseal (*Hydrastis canadensis*)

Active Ingredient: berberine, hydrastine

Mechanism & Benefits: It may inhibit CYP3A4 and it is also used as a diuretic. However, it is actually an aquaretic (allows only the excretion of water, not sodium and water).

Potential Side Effects & Precautions: It decreases heparin, coumadin, and blood sugar. It may also cause digestive disorders, hallucination, and delirium.[61] Because it is an aquaretic, edema may occur. If a patient is taking an antihypertensive agent, then the antihypertensive effect may be blunted, especially as sodium is retained.[39]

Grapefruit Juice

Active Ingredients: It occurs due to begamottin, maringenin flavonoids or furocoumarins; the action is immediate and lasts up to 24 hours.[11, 12]

Mechanism & Benefits: Although it is not an herbal, it does inhibit gut wall enzymes, especially the CYP3A4 enzyme.[12, 62]

Potential Side Effects & Precautions: Grapefruit juice increases the bioavailability of many substrates to immunosuppressives, particularly cyclosporine; the dihydropyridine calcium-channel blockers (amlodipine, nifedipine, nimodipine, nisoidipine, felodipine); statin antilipemics (lovastatin, simvastatin); amiodarone; CSA; and nonsedating antihistamines.[12, 63]These are drugs with high first pass metabolism in the gastrointestinal tract. Altered cardiac repolarization in poor metabolizers of terfenadine and increases in the QT interval have been reported when terfenadine was taken with grapefruit juice compared with water.[64] Grapefruit juice may also increase plasma concentrations of midazolam or triazolam, although clinical effects may be minor. Other types of calcium channel

blockers such as diltiazem are not affected by grapefruit juice. Syncope, muscle pain, and rhabdomyolysis have been reported; grapefruit juice can increase the absorption of lovastatin 30 times in the group that poorly absorbs.[12] It does not appreciably affect digoxin levels.[65] In healthy volunteers, it may increase concentrations of certain plasma estrogens.[62]

Kava (*Piper methysticum*)

Active Ingredient: Kavapyrones (kawain, kavaine, methysticine, etc.) have a half-life of about 8 hours.[13, 58]

Mechanism & Benefits: It may be important in the treatment of anxiety and increase barbiturate-induced sleep time; thus, it may also have dose-dependent effect on the CNS by potentiating GABA inhibitory neurotransmitters, especially in the amygdala, and decreasing excitatory neurotransmission.[13, 26]

Potential Side Effects & Precautions: It can cause a scaly dermatitis with chronic long-term use; in some patients, this will respond to increased intake of vitamin B.[66] Liver toxicity may be a special problem if there is a pre-existing liver problem or concomitant alcohol ingestion; CYP2D6 deficiency may be a risk factor for liver toxicity.[67] Jaundice, nausea, light-colored stools, fatigue, and stomach pain can occur.[68] Red eyes, tearing, and dilated pupils with a sluggish light response have been noted in some human subjects; a reduced near point of accommodation and convergence has also been reported.[66] Kava may cause coma if used with alprazolam.[26] Kava may worsen the symptoms of Parkinson disease.[38] It may have additive effects with other muscle relaxants, sedatives, anti-anxiety agents, and antidepressants.[38] There is a theoretic potential for prolongation of anesthesia with kava use.

Licorice (*Glycyrrhiza glabra*)

Active Ingredient: Glycyrrhizic acid inhibits 11-beta-hydroxysteroid dehydrogenase, 5-alpha and beta reductase; this allows excess cortisol to be accumulated.[69]

Mechanism and Benefits: Licorice is used to treat peptic ulcer and gastritis.

Potential Side Effects & Precautions: An episode of pseudoaldosteronism can manifest with hypertension, hypokalemia, hypernatremia, metabolic alkalosis, and weight gain secondary to edema; the hypertension can be severe and chronic but the other components disappear after a few days. Temporary visual problems may occur due to retinal blood vessel spasm and an acute myopathy can occur with chronic use. Licorice is the primary ingredient in smokeless (or chewing) tobacco and a common component of Chinese and Japanese herbals. [25] Licorice is contraindicated in many chronic liver conditions, renal insufficiency, hypertonia, and hyperkalemia. Potassium loss is enhanced with thiazide and loop diuretics. With potassium loss, sensitivity to glycosides (e.g., digoxin) increases.

Lily-of-the Valley Herb

Mechanism & Benefit: It is a cardioactive glycoside (positive inotropic effect on the myocardium, negative chronotrope) contraindicated with glycosides and potassium deficiency).

Potential Side Effects & Precautions: Side effects are nausea, vomiting, cardiac arrhythmia; simultaneous administration with quinidine, calcium, saluretics, laxative, and/or glucocorticoids enhance effects and side-effects. The herb is found in powder, capsule, solution, tincture, and liquid extract form.[34]

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

Active ingredient: Hyperforin is the most metabolically active ingredient currently recognized. However, the herbal is usually defined by hypericin, which was previously thought to be the most active ingredient; it is bioactive in vitro.[13] The half-life of various metabolites ranges from 9 to 43 hours.[58]

Mechanism & Benefits: St. John's wort is used for mild to moderate depression; it inhibits serotonin, norepinephrine, and dopamine reuptake in vitro but not in vivo in usual amounts. Use with or without a serotonin-reuptake inhibitor may create a central serotonin excess syndrome.[69, 70] It induces cytochrome enzymes (especially CYP450 3A) and P-glycoprotein; this, then, increases the elimination of drugs and affects 50% of drugs in the marketplace. Therefore, St. John's wort decreases the blood levels of cyclosporine, all currently marketed HIV protease inhibitors, warfarin, lidocaine, calcium channel blockers, digoxin, imatinib, theophylline, simvastatin, tetracycline, and serotonin receptor antagonists.[71, 72] It may only take two weeks of oral use of St. John's wort to cause a doubled clearance of alprazolam.[73]

Potential Side Effects & Precautions: St. John's wort can lower the blood levels of cyclosporine and induce rejection; it can also lower the blood levels of antiretroviral drugs and lead to loss of virologic response. Concomitant antidepressant use has been associated with hypertension, serotonin syndrome, or lack of effect.[69] Serotonin syndrome is characterized by headache, gastrointestinal upset, motor restlessness, autonomic and mental status changes.[41] St. John's wort decreases the efficacy of sildenafil so that increased amounts of sildenafil are prescribed; there has also been break-through bleeding, which affects the use of oral contraceptives and has been associated with pregnancy.[12] It also affects estradiol, and desogestrel.

St. John's wort rarely causes skin photosensitivity; however, it carries the potential for eye phototoxicity since there is uptake in the lens and growth inhibition of retinal pigment epithelial and choroidal endothelial cells in an animal study.[74] The dose of hypericum used in animal studies is 20 to 30 times the human dose for mild to moderate depression.[73]

Valerian *(Valerina officinalis)*

Active Ingredient: Many identified but two main categories: volatile oil containing valerianic acid and iridoids.

Mechanism & Benefits: valerianic acid increases GABA secretion and inhibits breakdown.[75]

Potential Side Effects & Precautions: Increased sedation with concomitant benzodiazepines may occur and adverse interactions may occur with tricyclic antidepressants.[12]

Yohimbe

Active Ingredient(s): various alkaloids including yohimbe and tannins.

Mechanism & Benefits: It may be a monoamine oxidase inhibitor as well as a pressor agent; it blocks presynaptic alpha$_2$-adrenergic receptors and decreases outflow of blood from the penis.[76]

Potential Side Effects & Precautions: Adverse interactions may occur in patients with hypertension, or those taking monoamine oxidase inhibitors.[25] Yohimbe may increase the risk of intraoperative hemodynamic instability.[3] An allergic dermatitis with eosinophilia has been reported and a lupus-like syndrome.[76] In moderate doses, yohimbe may increase systolic blood pressure in patients with orthostatic hypotension secondary to primary autonomic failure.[34]

INFORMATION FOR PATIENTS

The following material is excerpted from *An FDA Guide to Dietary Supplements*.[15]

- A healthy diet with a variety of fresh fruits and vegetables will have many overall benefits and may also contain many of the antioxidant vitamins and minerals.
- Consumers who use dietary supplements should always read product labels, follow directions, and heed all warnings.
- To help protect themselves, consumers should:
  - Look for ingredients in products with the U.S.P. notation that indicates that the manufacturer followed standards established by the United States Pharmacopeia.
  - Realize that the label term "natural" doesn't guarantee that a product is safe.
- Supplement users who suffer a serious harmful effect or illness that they think is related to supplement use should call a doctor or other health care provider.
- If shoppers find dietary supplements with labels stating or implying the product can help diagnose, treat, cure, or prevent a disease, they should realize the product is being marketed illegally as a drug and as such has not been evaluated for safety or effectiveness.
- The majority of supplement manufacturers are responsible and careful. But as with all products on the market, consumers need to be discriminating. FDA and industry have important roles to play, but consumers must take responsibility, too.

ADVERSE EVENT REPORTING

To further our understanding of the impact that nutritional supplement use has on patient health and well-being, Pamela S. Chavis, MD, has established a monitoring process to collect information about adverse events related to nutritional supplement use. A reporting form is included with the assessment and may be sent to the FAX number on the form.

MEDWATCH, the FDA Safety Information and Adverse Event Reporting Program, also collects information about adverse events related to dietary supplements. Reports to MEDWATCH are voluntary and can be made by phone (1-800-FDA-1088), fax (1-800-FDA-0178), or on the Internet (http://www.fda.gov/medwatch/report.htm).

ADDITIONAL RESOURCES

An 8 ½ inch by 11inch information poster on nutritional supplements for office use can be downloaded in PDF format for printing in black and white or color. Pamela S. Chavis, MD, and Mary Beatty-Brooks produced the poster for the McGuire Veterans' Administration Medical Center in Richmond, VA.

The American Society of Anesthesiologists (www.ASAhq.org) has helpful information for patients and physicians about dietary supplement use and anesthesia.

Additional Internet resources include:

- NIH Office of Dietary Supplements available at http://ods.od.nih.gov/
- FDA Consumer: *An FDA Guide to Dietary Supplements.* Available at http://www.cfsan.fda.gov/~dms/fdsupp.html
- Federal Trade Commission available at http://www.ftc.gov
- USDA Agricultural Research Service Phytochemical and Ethnobotanical Databases at http://www.ars-grin.gov/duke/
- The National Eye Institute at www.nei.nih.gov

CONCLUSIONS

The effects of herbals are diverse and can be adverse. Their use is disseminated throughout the population and merits observation. Yet patients do not readily offer information about nutritional supplement use to their physicians. If a surgical procedure is contemplated or untoward event occurs, it is important for the physician to ask the patient about any use of alternative medications. This will allow the patient and physician to discuss any potential for adverse interactions and plan for any discontinuation of the supplement before surgery.

The cost of using herbal supplements can be significant and is seldom covered by health insurance. The quality of supplements can vary by manufacturer and absorption can be affected by a variety of dietary factors.[77] Pesticides, herbicides, and other ingredients may contaminate herbal products.[77]

This assessment is not meant to cover every potential side effect that a nutritional supplement may cause but the ones of most importance to the physician-patient team. This assessment does not contain information on herbs used in other healing traditions, such as in Chinese medicine. Although this information will be updated periodically, it may not be complete on a specific supplement or problem. Health-related information changes frequently and therefore information contained in this assessment may be outdated, incomplete or incorrect. Very few randomized controlled clinical trials exist for the use of nutritional supplements. Much of the material in this assessment is drawn from studies of small series of patients and anecdotal information. Much of the material in print merits further scientific validation and verification. The Food and Drug Administration has not evaluated statements made about products.

The material in this complementary therapy assessment has not been reviewed or approved by the Board of Trustees of the American Academy of Ophthalmology and does not in any way constitute a guideline or policy of the American Academy of Ophthalmology. This material has been developed by the American Academy of Ophthalmology to inform its members.

DEVELOPMENT OF COMPLEMENTARY THERAPY ASSESSMENTS

Complementary, or alternative therapies, are a growing part of health care in America. Americans spend an estimated $14 billion a year on alternative treatments. Mainstream medicine is recognizing a need to learn more about alternative therapies and determine their true value. Most medical schools in the United States offer courses in alternative therapies. The editors of the *Journal of the American Medical Association* announced that publishing research on alternative therapies will be one of its priorities. The National Institutes of Health National Center for Complementary and Alternative Medicine has broadly defined complementary and alternative medicine as those treatments and health care practices not taught widely in medical schools, not generally used in hospitals, and not usually reimbursed by medical insurance companies. More scrutiny and scientific objectivity is being applied to determine whether evidence supporting their effectiveness exists.

In the fall of 1998, the Board of Trustees appointed a Task Force on Complementary Therapy to evaluate complementary therapies in eye care and develop an opinion on their safety and effectiveness, based on available scientific evidence, in order to inform ophthalmologists and their patients. A scientifically grounded analysis of the data will help ophthalmologists and patients evaluate the research and thus make more rational decisions on appropriate treatment choices.

The Academy believes that complementary therapies should be evaluated similarly to traditional medicine: evidence of safety, efficacy, and effectiveness should be demonstrated.[78-80] Many therapies used in conventional medical practice also have not been as rigorously tested as they should be. Given the large numbers of patients affected and the health care expenditures involved it is important

that data and scientific information be used to base all treatment recommendations. In this way, we can encourage high-quality, rigorous research on complementary therapies.[81, 82]

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Prepared by the American Academy of Ophthalmology Complementary Therapy Task Force

Author: Pamela S. Chavis, MD

Ivan R. Schwab, MD, Chair
Pamela S. Chavis, MD
Roger Husted, MD
Jeffrey Todd Liegner, MD
Harold P. Koller, MD
William F. Mieler, MD
Sayoko E. Moroi, MD, PhD
Denise Satterfield, MD
Peter R. Holyk, MD, Consultant

Academy Staff: Nancy Collins, RN, MPH
Flora Lum, MD

Approved by the Quality of Care and Knowledge Base Development Secretariat
November 10, 2003