Lesson S11: PreAnesthetic Assessment of the Patient Using Herbal Therapies – Part 2

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Needs statement

Herbal, supplemental and alternative therapies can have negative effects in presurgical patients. Patients infrequently view herbs as harmful drugs. The Food and Drug Administration (FDA) does not regulate herbal preparations in the same strict manner as pharmaceuticals and there is no control on the amount of active ingredients in most of these preparations. Anesthesiologists must be aware that drug interactions can occur, especially during the perioperative period. Physicians need to be equipped with the knowledge of potential problems so that patients may be appropriately advised.

This is the second installment of a two part series which will review the impact of herb therapy on the surgical population. Complications and drug interactions associated with specific herb therapies are addressed.

Learning Objectives

At the end of this activity, the participant should be able to:

1. List the most common herbs used for therapy in the United States.
2. Outline the prevalence of consumption of common herbs in the United States.
3. Specify the therapeutic uses of common herbs.
4. List the adverse effects of common herbs.
5. Identify drug interactions associated with common herbs.
6. Be conversant about perioperative considerations associated with herbs.
7. Cite interactions of herbs with specific anesthetics.
8. Discuss symptoms indicative of drug-herb interactions.
9. Describe methods of prevention and management of drug-herb interactions.
10. Identify reference sources where more information of herbs may be obtained.

Case History

During a preoperative evaluation, a 76-year-old Asian female scheduled for total hip replacement revealed that she was regularly ingesting a variety of herbs to treat depression and to simply season food. She possessed several capsules of Kava-kava and St John's Wort. She reported the use of ginger, ginkgo and ginseng daily. The patient stated that her surgeon and primary care physician were not informed about her regular use of these herbal substances as she did not regard them as medicine. Physical examination showed a mildly obese female weighing 90 kg with poor dentition and recent episodes of gingival bleeding. Preoperative laboratory tests showed a hemoglobin of 9.0 gm/dl. A bleeding time was found to be abnormal at 16 minutes. Both PT and PTT were elevated.

Introduction

There are more than 12,000 identified herbs with thousands of combination preparations available as over-the-counter therapeutic agents in the United States. The most popular are *Echinacea* (*Echinacea purpurea, Echinacea pallida and 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*), cranberry (*Vaccinium macrocarpon*), St. John's Wort (*Hypericum perforatum*), valerian (*Valeriana officinalis*) and feverfew (*Tanacetum parthenium*).[3] Vitamin preparations that incorporate herbs, mineral compounds, green and herbal teas and grapefruit extracts are readily available and widely consumed.

Following is a review of some of the most common herbs and their effects.

Echinacea

The *Echinacea* belong to the daisy family and grow throughout the North American plains, prairies, and woodlands. There are nine species of *Echinacea* but medicinal preparations are primarily derived from *Echinacea pallida* (pale purple coneflower), *Echinacea purpurea* (purple coneflower) and *Echinacea angustifolia* (narrow leaved coneflower).[16] Alkylamide and polysaccharide constituents of *Echinacea*

have shown significant *in vitro* and *in vivo* immunostimulation due to enhanced phagocytosis and nonspecific T-cell stimulation.[17] However, there are few well designed scientific trials validating the therapeutic effects of *Echinacea*. In one randomized, double-blind, placebo-controlled study involving 302 volunteers taking *E. angustifolia* and *E. purpurea* and placebo, the two *Echinacea* compounds had subjective beneficial effects with regard to upper respiratory infection (i.e., rates of infection were 36.7% in placebo group, 32% in *E. angustifolia* group and 29.3% in the *E. purpurea* group).[18] The observed trend toward a reduction of upper respiratory tract infections among those who ingested *Echinacea* failed to achieve statistical significance. Other trials have been conducted with similar outcomes. [19] *Echinacea* has also been used to promote wound healing.

The most commonly reported side effect of *Echinacea* taken orally is an unpleasant taste sensation.[20] Using *Echinacea* for more than 8 weeks may cause tachyphylaxis. Anaphylaxis is possible with a single dose since it there may be cross-sensitivity with other allergens, especially with the members of the sunflower family (*Asteraceae*).[16] This herb can be hepatotoxic if combined with other agents that impact liver function such as anabolic steroids, amiodarone, methotrexate and ketoconazole.[21] Flavinoids from *E. purpurea* are known to inhibit the hepatic cytochrome P-450 3A4 and sulfotransferase.[22] The metabolism of immunosuppressant and cancer chemotherapy may be altered. Use of *Echinacea* is contraindicated in systemic and autoimmune disorders.

Drug Interactions

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

Garlic

Garlic (*Allium sativum*) has been used for medicinal purposes for centuries. The active ingredient of garlic is allicin, a sulfur-containing compound that gives garlic its characteristic smell. Crushing the garlic clove activates the enzyme allinase, which converts allin to allicin.[16] Several studies have targeted its vasodilator and hypocholesterolemic activity.[23,24,25] Garlic derivatives are frequently used for antiplatelet, antioxidant and fibrinolytic effects. A meta-analysis of the results of 16 clinical trials demonstrated that garlic was effective in reducing total cholesterol by 12%.[26] Serum triglyceride levels were also decreased but HDL levels were unchanged. Other studies have found no improvement in serum lipid profiles of patients with hypercholesterolemia taking garlic.[27] The evidence supporting the use of garlic for hypertension is less substantial, with a few clinical trials showing modest decreases in systolic and diastolic blood pressure with the use of garlic supplements.[16] Decreased platelet aggregation induced by garlic has been described. One case reports spontaneous spinal/epidural hematoma in an 87 year-old male with platelet dysfunction related to excessive garlic ingestion.[28]

Drug Interactions

Garlic may augment the effects of warfarin, heparin, non-steroidal anti-inflammatory agents (NSAIDs), and aspirin and may result in an abnormal bleeding time that can potentially increase perioperative bleeding. This is a consideration for patients who suffer chronic pain and require a neuraxial block.

Ginger

Ginger (*Zingiber officinale*) has been described as an effective therapy for nausea, vomiting, motion sickness and vertigo. Anti-vertigo and anti-nausea effects of ginger have been observed in a study comparing patients taking ginger with those taking a placebo.[29] In a study comparing the effects of dimenhydrinate and ginger in the treatment of motion sickness, ginger exerted a superior anti-motion sickness response.[30] Ginger has a gastric mechanism, unlike the central nervous system mechanism of dimenhydrinate. Ginger has been demonstrated to be effective against nausea and vomiting of pregnancy as well as hyperemesis when compared with placebo, without evidence of significant side effects or adverse effects on pregnancy outcomes.[31] Two clinical trials concluded that ginger was ineffective in reducing the incidence of postoperative nausea and vomiting in patients undergoing gynecologic laparoscopic surgery.[32,33] Ginger has been found to be a potent inhibitor of thromboxane synthetase enzyme, which can prolong bleeding time.

Ginger root is often used as seasoning or a taste enhancer for other less palatable herbs.

Drug Interactions

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

Ginkgo

The extracts from the leaves of the *Ginkgo biloba* tree (or Maidenhair tree) have been used in traditional Chinese medicine for centuries.[16] The ginkgo tree can survive to an age of 1000 years and, in fact, withstood the atomic blast at Hiroshima. Asian civilizations have used this herb since 3000 BC to cure many ailments. It was first used in the United States around 1780 but it was not until the 1980's that the therapeutic value of ginkgo was studied.[2] The use of ginkgo is on the rise in the United States and it is listed as one of the best selling herbs on the national market, with sales in excess of $300 million. The most important components are flavinoids, terpenoids, and organic acids.[16] Metabolic pathways vary with different compounds. Thus far, four preparations of ginkgo have been used in clinical trials, namely tebonin, tanakan, rokan and kaveri. The extract from the first three forms has been classified as EGb 761.

Ginkgo has been advocated as an antioxidant, a circulatory stimulant, and is recommended for the treatment of intermittent claudication, tinnitus, vertigo, memory enhancement, and sexual dysfunction.[2] A large placebo-controlled, double-blind, randomized trial of EGb 761 studied the effectiveness of ginkgo in patients with dementia and concluded that ginkgo extract was capable of stabilizing and modestly improving cognitive performance and social functioning ability.[34] Further, ginkgo may improve the symptoms of intermittent claudication.[35] Study subjects using ginkgo experienced improved claudication distance and reduced pain in their lower extremities. The herb has an anti-inflammatory effect and also has the potential to inhibit platelet-activating factor and modulate nitric oxide. [36,37] In rabbits with spinal ischemia-reperfusion injury, administration of ginkgo leaf extracts was associated with increased hind limb movement.[38] The beneficial effects were attributed to scavenging of oxygen free radicals.

Ginkgo biloba is considered to be relatively safe with few side effects including mild gastrointestinal upset and headache. However, a few disturbing case reports have been published. Spontaneous hyphema (bleeding from the iris in the anterior chamber of the eye), subarachnoid hemorrhage, and spontaneous bilateral subdural hematomas have been described in persons using *Gingko biloba*. [39,40] Of additional concern is that the ginkgo toxin found in both the ginkgo leaf and seed is thought to be neurotoxic.[41]

Drug Interactions

Although there are no placebo-controlled double-blind investigations of ginkgo-induced abnormal bleeding, concomitant use with aspirin, or any NSAIDs and anticoagulants such as warfarin and heparin, is not recommended as ginkgo may increase the potential to bleed. Concomitant use with anticonvulsant drugs (e.g. carbamazepine, phenytoin, and phenobarbital) and tricyclic antidepressants may decrease their effectiveness.[10] Ginkgo may also cause hypertension when combined with a thiazide diuretic and coma when combined with trazodone.

St. John's Wort

Known colloquially as St. John's Wort, *Hypericum perforatum*, is approved in Germany for the treatment of numerous ailments including anxiety, depression, sleep related disorders and vitiligo. *Hypericum* has also been used as a deep violet-red dye for wool and silk. The herb is also known as hardhay, amber, goatweed, klamath weed and tipton weed. The Greek name, Hypericum, means "over an apparition" because of the belief that the herb repels evil spirits. Active compounds include, naphthadihydrodianthrones, particularly hypericin and pseudohypericin; and flavinoids including quercitrin, rutin and hyperin.[2]

The mechanism of action is controversial. *Hypericum* extract inhibits isoforms of monoamine oxidase *in vitro*, but this has not been observed in *in vivo* experiments.[42] *In vitro* studies have shown inhibition of GABA receptors by *Hypericum*, which suggests a mode of action for the antidepressant effects.[43] However, additional *in vivo* studies are needed to confirm this observation. Researchers postulate that serotonin receptor inhibition may be the underlying mechanism for the herb's antidepressant action.[44] A meta-analysis showed St. John's Wort, compared to a placebo, shows promise in the treatment of mild to moderate depression. Further studies with standardized variables are needed.[44]

The most prominent adverse effect of St. John's Wort is photosensitivity, attributable to the hypericin component. Other side effects include dry mouth, dizziness, fatigue, constipation and nausea. There have not been any reports of impact on cardiac conduction, although if used concomitantly with a selective serotonin reuptake inhibitor (SSRI), a potential serotonergic syndrome may occur characterized by tremors, hypertonicity, myoclonus, autonomic dysfunction, hallucinosis, hyperthermia and even death.[54,16]

Drug Interactions

Concomitant use of St. John's Wort is not recommended with drugs that cause photosensitivity (e.g. piroxicam and tetracycline hydrochloride); monoamine oxidase inhibitors (e.g. phenelzine); or b-sympathomimetic amines (e.g. ma huang, pseudoephedrine hydrochloride). The herb lowers the blood concentration of cyclosporine, amitriptyline, digoxin, indinavir, warfarin, and theophylline.

Intermenstrual bleeding, delirium, and mild serotonin syndrome have occurred when the herb is used with oral contraceptives, loperamide or selective SSRIs such as sertoline and paroxitine.

Ginseng

Several varieties of ginseng are available including homegrown American ginseng (*Panax quinquefolius*), Chinese ginseng, Korean ginseng (*Panax ginseng*) or Tienchi (*Panax notoginseng*). American and Asian varieties of ginseng are nutritionally similar. It should however be noted that Siberian ginseng (*Eleutherococcus senticosus*) belongs to a different genus.

The active compound in *Panax ginseng* is ginsenoside.[2] In ancient times, the herb was used as an aphrodisiac, anti-aging and energy-boosting tonic. Athletes use it to increase "energy levels" and as an antioxidant.[46] The herb is extremely popular and has been labeled as an "adaptogenic, augmenting adrenal steroidogenesis via a centrally mediated mechanism".[47] Ginseng's immunomodulatory effects have been described and studies have shown a ginseng-induced hypoglycemic effect. This hypoglycemic effect has been attributed to ginsenoside Rb2 and panaxans I, J, K, and L .[48,49]

Adverse effects include hypertension, insomnia, headache, vomiting, and epistaxis.[50] Stevens-Johnson syndrome, postmenopausal vaginal bleeding, mastalgia and diffuse breast nodularity have been associated with the use of this herb.[51,52] Ginseng should not be used by pregnant or lactating women, or patients with cardiovascular disease.[2,10] One fatality was associated with ingestion of ginseng mixed with ma huang.[53] Ginseng reportedly interacted with warfarin leading to clinically relevant coagulation modulation in an isolated case.[54] It has been surmised that the herb may contain antiplatelet components.

Drug Interactions

The use of ginseng should be avoided in patients taking warfarin, heparin, NSAIDs and aspirin. Ginseng can cause hypertension. Patients are often volume depleted and the vasodilatory effects of anesthetics can result in intraoperative hypotension. Manic episodes and coma have been reported when ginseng is combined with monoamine oxidase inhibitors (e.g. phenelzine sulphate).[55] Ginseng should be avoided or cautiously used in patients taking insulin or oral hypoglycemic medications because of its hypoglycemic effects. Blood glucose levels should be monitored perioperatively in patients at risk (e.g. neurosurgical patients receiving steroids, or patients with diabetic end stage renal disease).

Kava-kava

Kava-kava (*Piper methysticum*) is primarily utilized for its anxiolytic properties. The herb grows in Polynesia, Melanesia and Micronesia and has long been used in ceremonial rituals of Pacific Islanders in the form of a fermented liquor. Kava lactones are the active compounds.[56] Kava-kava has also been used to treat gonorrhea and skin disorders.[57] The herb is banned in Europe because hepatotoxicity resulted in the need for liver transplant in more than 20 patients.[58] Kava-kava has been attributed with anesthetic, analgesic, anti-convulsive, anti-fungal, sleep inducing and spasmolytic properties. Antinociceptive effects produced by kava-kava may be similar to local anesthetic responses.[60] Kava-kava can cause visual alterations, ichthyosiform dermapathy, and hallucinations.[2,59] The inhibition of noradrenaline may contribute to the psychotropic qualities of the herb.

Drug Interactions

Ethanol can increase the hypnotic effect of kava-kava. Patients with endogenous depression can have an increased risk of suicide with kava-kava.[56] It can also potentiate the effects of barbiturates and benzodiazepines resulting in excessive sedation. Kava-kava has also been shown to increase the "off" periods in Parkinson patients taking levodopa and can cause a semi comatose state when given concomitantly with alprazolam.

Feverfew

Feverfew (*Chrysanthemum parthenium, Tanacetum parthenium*) is an ornamental medical herb that is also known as featherfew, featherfoil, midsummer daisy, bachelor's button, wild chamomile and compositae.[2] Its name is derived from the Latin *febrifugia* meaning, "fever reducer". Parthenolide is the active compound found in the herb. Feverfew is commonly used is for treatment of migraine headaches, although studies show mixed results on its effectiveness. One double-blind placebo-controlled trial found a 70% reduction in migraine frequency in patients taking feverfew.[61] In a randomized controlled trial using a different preparation of feverfew, migraines were not preempted.[62] Like many herbs, it is difficult to quantify the amount of active ingredient in different preparations. For this reason, clinical trials performed with herbs often lack precision.

Feverfew inhibits serotonin release from aggregating platelets. This may be related to inhibition of the release of arachidonic acid via a phospholipase-linked mechanism.[63] The herb has been found to reduce prostaglandin production by 86% to 88% without inhibiting the cyclooxygenase enzyme.

Adverse effects include apthous ulcers and gastrointestinal irritability. Rebound headache may be associated with cessation of the herb.[64] Feverfew is not recommended for children, pregnant patients or nursing mothers. Post feverfew syndrome is characterized by nervousness, headaches, insomnia, arthralgias, joint stiffness and fatigue.

Drug Interactions

Feverfew can inhibit platelet activity and should be avoided by patients taking medications such as, heparin, warfarin, NSAIDs, aspirin and vitamin E. Tannin-containing herbs like feverfew can reduce the bioavailability of iron preparations.

Ma huang (Ephedra)

Shen Neng's classic text on medicinals listed ma huang (*Ephedra sinica*) as one of 365 herbs, as early as the 1st century AD. It is traditionally used for treatment of the common cold, flu, various allergic symptoms, bronchitis, low blood pressure, fever, asthma, arthritis and fluid retention. Native Americans have used *Ephedra* as an external application for sore healing.[2] It acts as a sympathomimetic agent, and possesses positive ionotropic and chronotropic responses. *Ephedra* also has bacteriostatic and antitussive actions. It is a cardiovascular stimulant (acts as an a- or b-adrenergic agonist) and is a potent bronchodilator.[65] Because it increases metabolic rate, *Ephedra* is contained in many over-the-counter weight reduction plans.

Adverse effects include hypertension, tachycardia, cardiomyopathy, cardiac dysrhythmias, myocardial infarction, cerebrovascular accidents, seizures, psychosis and/or death. Numerous fatalities have been linked to its use more than likely due to overdose of the active ingredient because of the lack of standardization in the formulation.[2,66] Sale of the herb was banned in the United States. However, surveillance cameras have indicated that it was not removed from shelves of herbal stores completely and can still be found in combination with other herbal preparations, especially in cold remedies.

Drug Interactions

Ephedra can interact with volatile general anesthetic agents (e.g. halothane) and cardiac glycosides (e.g. digitalis) to cause cardiac dysrhythmias. With general anesthesia, patients taking *Ephedra* can have severe hypotension treatable with phenylephrine instead of ephedrine. Use of *Ephedra* with phenelzine or other monoamine oxidase inhibitors may result in insomnia, headache, and tremulousness. Concomitant use with oxytocin can cause hypertension.

Other commonly used herbs

Several other herbs have significant perioperative implications.

Goldenseal is taken as a mild laxative and anti-inflammatory. It is widely used for intestinal problems, and can increase blood pressure or cause electrolyte imbalance from diarrhea. Saw palmetto, taken for urinary difficulties, may interact with other hormone therapies. Valerian, used for its sedative and muscle relaxant effects, may increase the effectiveness of antiseizure medications and prolong action of other sedatives.

Although not an herb, colloidal silver is touted for its ability to treat infectious diseases and is available in preparations that may be inhaled or ingested. Long term use has been associated with development of a gray hue to the skin that is not reversible. Also, nasal inhalation may cause long term pulmonary problems. Colloidal silver products also may interact with medications, including penicillamine, quinolones, tetracycline and thyroxine medications.

Green tea is said to improve cognitive function, treat gastrointestinal distress and headaches. It is used as a diuretic and in combination products for weight loss. It contains considerable amounts of caffeine and ingestion of more than five cups per day (300mg caffeine) has been associated with several adverse effects such as headache, insomnia, liver dysfunction, and tachyarrhythmias. When taken by infants, impaired iron metabolism and microcytic anemia have been reported.

Grapefruit juice contains several substances known to inhibit hepatic microsomes and cytochrome P450 3A4. It can reduce cholesterol levels and hematocrit. Grapefruit juice increases the bioavailability of midazolam, buspirone, caffeine, calcium channel blockers, carbamazepine, carvedilol, cisapride, clomipramine, cyclosporine, estrogens, lovastatin, losartan, quinidine, terfenadine and warfarin.

Anesthesia and Herbal Medicine

There are only a small number of case reports relating to interactions of herbal medicine with anesthetics. Because of the widespread use of herbs, there is a need for well-designed scientific studies to elaborate the anesthetic responses in patients taking over-the-counter herbs.

In one case report, a 42-year-old obese male patient had a cardiac arrest, 20 minutes after receiving epidural anesthesia.[67] Following successful resuscitation, blood samples were taken which revealed low plasma renin and aldosterone levels. It was determined that the patient was taking an herbal preparation containing ethoxybenzamide (an NSAID) for one and a half years. Cardiac arrest was attributed to NSAID-induced hyporeninemic hypoaldosteronism superimposed on epidural anesthesia-induced sympathectomy.

HERBAL MEDICATIONS AND ANESTHESIA

HERB	EFFECT
Echinacea	offsets immunosuppression inhibits hepatic microsomal enzymes
Ephedra	interacts with inhalation anesthetics
Feverfew	inhibits platelet activity
Garlic	augments heparin, NSAIDs
Ginger	increases bleeding time
Ginseng	causes hypertension, hypoglycemia reacts with MAO inhibitors
Kava-kava	reacts with ethanol, excessive sedation
St John's Wort	reacts with MAO inhibitors, tetracycline

Huatuo reconstructive pill (HRTP), a traditional Chinese medicine for treating cerebral palsy, has been studied in anesthetized animals.[68] Carotid blood flow was selectively increased without changing vascular resistance of the hind limb. The internal carotid blood flow reached as high as 173% of the control level. A positive inotropic action was demonstrated with an increase in left ventricular pressure and an increase in cardiac output without changes in heart rate, blood pressure, electroencephalogram, electrocardiogram, or respiration.

Management of the case presented

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

Summary

Herbal medicines have enormous presence in the United States with increasing acceptance as complementary medicine. Because of the expense of Western pharmaceuticals and restrictions of health insurance coverage, the use of herb treatments is likely to become more prevalent. Herbs are categorized as "supplements" by the Food and Drug Administration. Under the Dietary Supplement and Health Education Act of 1994, supplements do not require proof of efficacy. Further, safety does not have to be demonstrated and there are no standards for quality control. This lack of validation increases the risk of adverse effects of these herbs. And there is little motivation for the manufacturers of "natural products" to conduct randomized, placebo-controlled, double-blinded clinical trials to unequivocally prove the safety and efficacy of these drugs. Physicians should never underestimate the potential risks associated with the use of herbs. Within the last two decades, there have been reports of many serious complications and more than 100 herbogenic deaths. Patients have required renal dialysis, renal transplantation and hepatic transplantation after taking botanicals.

Internists must inquire about the patient's use of herbal products. In addition, the education of each patient regarding the serious, potential drug-herb interactions should be a routine component of preoperative assessment. The American Society of Anesthesiologists (ASA) recommends that all herbal medications should be discontinued 2-3 weeks prior to an elective surgical procedure. If the patient is not sure of the contents of the herbal medicine, he/she should be urged to bring the container so that an attempt can be made to review the contents of the preparation. While such an action holds some promise in the elective setting, emergency care should be based on a thorough drug-intake history from the patient or a relative, if possible.

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

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Post-test

1. St John's Wort:

a. may act as an SSRI
b. causes photosensitivity
c. is effective for depression
d. all of the above

2. Which of the following herbs has been shown to possess significant in vitro and in vivo immunostimulation properties ?

a. Garlic and ginseng
b. Echinacea
c. St John's Wort and Kava kava
d. Ginkgo

3. All of the following herbs interfere with platelet function except:

a. Ginger
b. Garlic
c. *Ginkgo biloba*
d. Feverfew

4. Which of the following herbs can cause hypertension?

a. *Echinacea angustifolia*
b. *Allium sativum*
c. *Ephedra sinica*
d. Ginger

5. Which herb inhibits hepatic microsomal enzymes?

a. Ginseng
b. Garlic
c. Kava kava
d. *Echinacea*

6. The least likely adverse effect of *Ginkgo biloba* is:

a. increased bleeding time
b. memory loss
c. mild gastrointestinal upset
d. headache

7. Ma huang does not usually cause:

a. bronchoconstriction
b. tachycardia
c. hypertension
d. cerebrovascular accident

8. In the United States, herbal medicines:

a. are categorized as supplements by the FDA
b. do not require proof of efficacy or safety
c. are increasing in use
d. all of the above

9. Ginseng:

a. may have a hyperglycemic effect
b. may increase bleeding
c. is classified according to potency
d. does not have any active ingredients

10. Kava-kava

a. is widely used in Europe
b. has anxiolytic effects
c. is used for its antipsychotropic effect in the Pacific Islands
d. improves vision