69 Herbal Medicine

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DRUG LIST

Herbal therapies have become an integral part of the American health care scene. Since 1991, public use of herbal products has increased quite markedly, with over $5 billion spent annually. This does not include the many (up to 25%) pharmaceutical products used in conventional practice that originally were, and in some cases still are, derived from plants (Table 69.1). The perennial appeal of herbs may stem from their "natural" origin, giving them the reputation of being somehow safer and better tolerated than prescription drugs. In addition, they are available without prescription, often at much lower cost. For much of the world's population, herbal treatments remain the first and sometimes the only available treatment. Proponents of herbal therapy also state that the multiple compounds found in most herbal preparations have the advantage of acting *synergistically;* that is, they act in concert to produce a more enhanced effect than would a single isolated component. An example is St. John's wort (*Hypericum perfoliatum*), which contains not only hypericin, the ingredient it is usually standardized for, but also hypaphorine and a variety of other compounds. It is now believed that these other ingredients, far from being extraneous, contribute significantly to the herb's effectiveness.

The study of natural product medicines is termed *pharmacognosy,* which includes the study of herbal medicine. The resurgence of herbal medicine use has once again made pharmacognosy extremely relevant to the medical curriculum.

HERBAL MEDICINE TRADITIONS

The popular *western herbalism* discussed in this chapter is one of many philosophical systems of herbal treatment. It is also sometimes described as *eclectic,* since it has drawn on many other traditions, including the native American and Chinese. *Chinese traditional medicine, Ayurvedic* (Indian), and *Tibetan* traditions use complex herbal recipes and nutrition to achieve "balance" in the ill patient. Although these practices are most commonly found in ethnic populations, they are also becoming popular in some western complementary and alternative circles.

Homeopathic treatments frequently bear herbal names and are often confused with allopathic herbal

TABLE 69.1 Plant-Derived Medicines

Active Ingredients	Botanical Source
Aspirin (acetylsalicylic acid)	Willow bark (salicylic acid)
Atropine	Belladonna nightshade
Capsaicin	Pepper plant
Colchicine	Autumn crocus
Digitalis	Foxglove
Morphine	Opium poppy
Pilocarpine	Jaborandi tree
Podophyllin	Mayapple root
Quinine	Cinchona bark
Reserpine	Indian snake root
Taxol	Pacific yew tree bark
Vincristine, vinblastine	Madagascar periwinkle

TABLE 69.2 Herbal Formulations

Formulation	Means of Preparation
Infusion	Near-boiling water poured on herb for 5–10 minutes
Tea (tisane)	Infusion of aromatic herbs
Decoction	Simmer herb for 15 minutes, then strain
Maceration	Steep herb in room-temperature water
Tincture	Steep herb in ethyl alcohol and water
Fluid extract	1 part herb to 1 part ethyl alcohol
Glycerin extract	Steep herb in glycerin–water mix
Juice	Juice expressed by crushing herb
Inhalation	Breathe in vapor from heated herb mix
Oil	Steep herb in olive or other plant oil
Ointment	Herb salve made with lanolin or beeswax
Lozenge	Herb preparation that dissolves in the mouth
Powder	Dried powdered herb
Tablet	Compressed herb material in pill form
Capsule	Encapsulated herbal material
Syrup	Concentrated sugar solution to preserve infusion
Compress	Cloth soaked in herbal solution
Poultice	Application of moist herbal paste

preparations. The difference is that homeopathic remedies are serially diluted and shaken until they may lack any molecule of the original herb ingredient. Therefore, there is no risk of pharmacological toxicity from a homeopathic preparation. *Bach's Flower Remedies* are a homeopathic variation in which flower essences are created by floating flowers in sunlit water. These essences are usually intended as remedies for emotional and spiritual rather than specific physical complaints.

Aromatherapy uses a variety of fragrant plant oils to treat mood or physical problems either topically (as an adjunct to massage) or through inhalation. Some of these oils are quite potent, and if not used in proper dilution, they may cause skin irritation or contact allergy. Toxic ingestions are also possible.

Herbs from these traditions often are administered in a confusing array of preparations (Table 69.2). In the U. S. market, tablet and capsule formulations are the most popular, while overseas, *teas* or *infusions* of herbs are the most widely used. *Tinctures* consist of an herb steeped in a mix of alcohol and water, and *extracts* consist of one part herb to one part ethyl alcohol. The alcohol content can be a concern, particularly with children. Some of these products have been withdrawn by the U. S. Food and Drug Administration (FDA) for this reason but may still be available outside the United States.

POTENTIAL CONCERNS

Detractors of herbal medicine use have legitimate concerns about dosage variability, possible toxicity and adulteration, herb–drug interactions, and above all, lack of FDA regulation. Far from being intrinsically harmless, many pharmacologically active plant alkaloids and other compounds are natural defensive poisons; their very effectiveness may be an unanticipated consequence of their adaptive toxicity to grazing animals and insects. Thus, herbal products like digitalis, while quite "natural," may also be dangerous or even fatal in overdose. Other herbs may not be superior to better-researched pharmaceuticals, or they may delay the use of more effective therapy. While herbal research has understandably lagged far behind that of patented medications, a surprising number of clinical trials exist, although some of them are fraught with methodological problems and much of the data is foreign and therefore not readily accessible to U. S. physicians. There is also the frustrating problem of interpreting conflicting research results; it is possible to assemble impressive arrays of studies both supporting and questioning the effectiveness of a particular herbal product. These conflicting findings may result from flawed study design, the use of differing preparations, or different study end points. Unfortunately, despite the recent increase in herb research, significant gaps in knowledge remain. An additional concern is that few if any available studies have been conducted on pregnant women or children.

Some herbal preparations, particularly some unbranded Asian imports, have been found to contain inactive fillers or *adulterants*. In one assessment, 24% of imported herbs were found to contain ingredients not on the label. These included specific medications (aspirin, caffeine, diuretics, and even benzodiazepines), not to mention heavy metals, such as lead. Some Asian formulations may also contain animal components. Therefore, it is advisable to buy only products that list the following information: botanical name or names,

parts used, expiration date, batch or lot number, and the manufacturer's name and address.

Of special concern today are the possible *herb–drug interactions* with which patients and their health care providers must be familiar. Some herbs, such as ginkgo, garlic, ginger, chamomile, horse chestnut, and feverfew, can prolong bleeding time and should be avoided with coumadin and antiplatelet regimens. It is also necessary that they be stopped 2 weeks prior to surgery. Other herbs, including kava, St. John's wort, and valerian, also must be discontinued prior to surgery because they can unpredictably alter the effects of common anesthetics. *Panax* ginseng may cause blood pressure fluctuations, and some herbs, notably St. John's wort, may lower the blood levels of many coadministered medications. For this reason, it is critical for consumers and their health care providers to maintain an open dialogue about herb use; the use of over-the-counter herbs and supplements should be inquired about when obtaining a medical history. Patients are frequently reluctant to discuss their herb use either because they fear disapproval or because of the all too often correct perception that the provider is not knowledgeable enough to warrant giving the information. *Blanket condemnation of herb use often has the counterproductive effect of terminating any further communication between physician and patient.*

REGULATORY ISSUES

The explosion in popularity of herbs dates to the *Dietary Supplement Health and Education Act of 1994* (*DSHEA*), in which the FDA recognized herbal preparations as dietary supplements outside of its direct regulatory control. The act was a compromise between the FDA and manufacturing lobbies brought about in large measure by increased public demand for herbal products. Instead of FDA regulation, these products now fall under the far less stringent Current Good Manufacturing Practice in Manufacturing, Packaging or Holding Human Food regulations. Unlike prescription pharmaceuticals, which must be proved safe and effective before being marketed, supplements do not have to be either safe or effective as long as they avoid therapeutic claims on the label. Neither are they policed in regard to delivering accurate doses, although some consumer-oriented organizations, such as *Consumer Lab* (www.ConsumerLab.com), are starting to hold manufacturers more accountable through random testing and reporting of their results. Supplements are permitted to have "*structure–function*" statements on their label stating only the product's supposed physiological function. For instance, an Echinacea product label might read "supports immune function" but may not claim to prevent or abort the common cold. The FDA recommended in 1999 an improved dietary supplement labeling system with a supplement facts panel that is being gradually adopted by the industry. Future legislation may further tighten the quite lax U. S. regulatory environment. Unsafe herbs (Table 69.3) also will be increasingly restricted.

TABLE 69.3 Potentially Toxic Herbs

Herbal Preparation	Type of Toxicity
Aristolochia	Nephrotoxicity
Bloodroot	General toxicity
Chaparral tea	Liver toxicity
Coltsfoot tea	Possible carcinogen, liver toxicity
Comfrey tea	Liver toxicity
Ephedra (ma huang)	Arrhythmias, stroke, elevated blood pressure
Lobelia	Nervous system toxicity, respiratory paralysis
Pennyroyal	CNS stimulation
Sassafras (safrole) tea	Carcinogen
Yohimbe	CNS stimulation, psychosis

The European system differs from that of the United States in that the manufacture of the more pharmacologically active herbs is for the most part regulated and is much more widely accepted by the medical community. Many health care providers routinely prescribe herbal treatments either alongside or in place of more conventional medications. The German government's *Commission E* publishes a set of herbal monographs that not only officially sets the standard for that country but has also become a widely respected clinical reference throughout the world.

HERBAL PREPARATIONS

Echinacea

The purple coneflower *Echinacea purpura,* and its close relatives, *E. angustifolia* and *E. pallida,* are the source of the herb Echinacea, which is widely popular as a nonspecific immune stimulant. These perennials are native to the prairies of North America and are now widely grown garden ornamentals. The root and aerial parts of the plant are the portions used, and the preparation's potency can be verified by the transient tingling sensation produced when it is tasted. Echinacea contains alkamides, caffeic acid esters (echinacoside, cichoric acid, caftaric acid), polysaccharides (heteroxylan), and an essential oil. Some echinacea products are standardized for their *echinacoside* content. In the past, adulteration with American feverfew (*Parthenium integrifolium*) was common. Echinacea is now sold either by itself or in combination with golden seal or zinc for the treatment of colds and influenza.

Mechanism of Action

Echinacea extracts appear to stimulate the number and activity of immune cells (i.e., increasing physiological levels of tumor necrosis factor and other cytokines)and to increase leukocyte mobility and phagocytosis. The extracts also have antiviral and antiinflammatory properties and inhibit bacterial hyaluronidase.

Indications

There are numerous studies on echinacea in the literature, many of which indicate either an in vitro immune stimulation or a significant clinical reduction in the severity and duration of upper respiratory viral symptoms, especially when taken early in the onset of symptoms. Despite several of these meta-analyses concluding that echinacea is an effective immunomodulator of acute infection, there is still controversy as to the extent of its clinical effectiveness. A number of trials now clearly indicate that echinacea is unlikely to be effective in the prevention of colds, even if it may slightly shorten their course.

In vitro antiinflammatory effects have been documented, and the herb has a long history of being used externally for wound healing, psoriasis, and the reduction of skin irritation. Although there are a few small positive studies, the available evidence is not yet conclusive in regard to clinical use.

Adverse Reactions, Contraindications, and Interactions

Echinacea appears to be a very safe herb, producing only minor gastrointestinal (GI) side effects and an occasional allergic reaction, usually in atopic patients already sensitized to other members of the Compositae plant family. Anaphylaxis has occurred rarely. Use in HIV is discouraged because of the concern that long-term therapy may eventually suppress the immune system.

It is recommended that echinacea not be taken by anyone for more than 8 continuous weeks, and most clinical use is under 2 weeks' duration. Echinacea has not yet been shown to be safe in pregnant or breast-feeding women and small children. No specific herb–drug interactions are reported, but for theoretical reasons those taking immunosuppressant drugs should avoid echinacea.

Dose

Usually echinacea is given as a capsule, but it is also available as an alcohol-based tincture. The use of echinacea tea is less desirable, since not all of the components are water soluble. Unfortunately, there are significant differences in the potency of commercially available supplies, depending on the plant species and the part and age of the plant used.

Conclusion

While it is still controversial, there is some evidence that echinacea stimulates the immune system and may mitigate some of the symptoms of viral infection. However, it does not appear to be helpful in *preventing* viral infections, and long-term use should be avoided.

Feverfew

Feverfew (*Tanacetum parthenium*) is a common European composite herb with daisylike white flowers now widely naturalized in the United States. While its name (a corrupted version of the Latin *febrifugia*) indicates a long history in herb lore, feverfew's current popularity is due to its use in the prevention and treatment of migraines. Feverfew has also been used for rheumatoid arthritis and numerous other conditions with far less substantiation. The leaves contain sesquiterpene lactones, including *parthenolide,* which is thought to be the most active and important ingredient. Feverfew preparations are frequently standardized for parthenolide content, which can vary substantially depending on time of harvest (levels drop after seeds form) and other factors. Most studies have used feverfew standardized to 0.6 to 0.7% parthenolide; the value of leaves containing less than 0.2% parthenolide is questionable.

Mechanism of Action

Parthenolide inhibits serotonin release, an action that is thought to be a likely source of its effectiveness in migraine. Extracts have also been shown to reduce the production of prostaglandins (another possible mechanism) and leukotrienes. Interestingly, *melatonin* has been identified in feverfew, a possibly significant observation, since chronic migraines have been associated with low melatonin levels.

Indications

At least three studies have demonstrated that feverfew (dried leaf, not extract) can reduce the frequency and severity of migraine headaches, although one study failed to find any significant difference from placebo. Prophylaxis appears to be more effective than acute treatment. There is also a consensus that feverfew is probably less effective than conventional migraine prophylaxis, although it may have a role as a second-line option. Although feverfew has also been used for rheumatism, it has never been verified to be effective in clinical trials.

Adverse Reactions, Contraindications, and Interactions

Although feverfew appears generally safe in nonpregnant adults, the use of fresh leaves has caused *mouth irritation* and even ulceration. This is far less likely to oc-

cur when the herb is encapsulated. *Allergic reactions* (contact dermatitis) have occurred with topical use in sensitized individuals, and ingestion may also produce allergic reactions in people with preexisting allergies to members of the Compositae family. Feverfew has caused contractions in term pregnancy and has been implicated in cattle abortions and so should be avoided in pregnancy and lactation. A *feverfew withdrawal syndrome* consisting of joint pain and muscle stiffness may occur following abrupt discontinuation. Theoretically, because of its antiprostaglandin effects, feverfew should not be coadministered with *anticoagulants* or *antiplatelet drugs.*

Dosage

For migraine prophylaxis: 50 to 125 mg per day with food, preferably in capsule form to prevent mouth irritation.

Conclusion

Feverfew may be considered as an *alternative migraine prophylaxis* regimen in patients failing to respond to conventional therapy. It has not been shown to be effective for rheumatoid arthritis. There is insufficient evidence to support its use in other conditions.

Garlic

Garlic (*Allium sativum*) is an ancient culinary and medicinal herb related to the onion and reputed to have many health benefits. Today it is popularly used to lower cholesterol and blood pressure and is even reputed to reduce the risk of cancer. It is also taken for its antimicrobial effects. The active ingredient, *allicin,* is the source of garlic's famous odor, and many sulfur-containing garlic constituents are derived from it. Odorless *alliin,* found in the garlic bulb, is converted to allicin by the enzyme *allinase,* which is released by chopping or cutting. Aged or cooked garlic has less odor but also much less active allicin.

Mechanism of Action

Garlic clearly has *antithrombotic* properties. Ajoene (an allicin metabolite) and methyl allyl trisulfide inhibit platelet aggregation. Garlic may promote *vasodilation* by relaxing smooth muscle, and it may *reduce low-density lipoprotein* (*LDL*) *oxidation.*

Indications

Some studies support garlic having a modest but significant effect on lowering total cholesterol, LDL cholesterol, and triglycerides and raising high-density lipoprotein (HDL) cholesterol. More recent studies have found no significant effect, even though similar preparations and doses were used. Therefore, the effectiveness of garlic for this indication remains unresolved. Likewise, some *blood pressure* studies have shown a modest reduction in diastolic more than systolic blood pressures, while others have not.

The antifungal effect of allicin in fresh garlic extract has been demonstrated against cryptococcal meningitis and a variety of yeasts and fungi. However, this effectiveness appears diminished in commercial preparations. Fresh but not aged garlic also appears to have activity against *Escherichia coli, Staphylococcus aureus,* and a variety of bacteria and viruses. Topical use also appears to be effective, albeit with occasional local irritation being produced. The high oral dosages of fresh garlic required for *antimicrobial* treatment may make clinical use less feasible due to odor and side effects. Garlic has been shown to reduce cancer susceptibility in mice, but epidemiological studies in human colorectal and other cancers are mixed.

For lipid reduction, garlic is used at 600 to 900 mg daily, usually divided into three doses, or 4 g fresh garlic or 8 ml of garlic oil daily.

Adverse Reactions, Contraindications, Interactions

Garlic can cause heartburn, nausea, and loose stools at high doses, especially in those unaccustomed to it. Its most characteristic and troublesome side effect, however, is persisting *breath odor,* which no amount of tooth brushing will eradicate. Allicin and its odoriferous metabolic products are actually released into the lung alveoli and exhaled.

Allergic contact dermatitis and even burns from prolonged skin contact with the cloves have been reported. Systemic allergy with bronchospasm or hives from ingestion occurs rarely. There is some concern that chronic high doses may lead to decreased hemoglobin production.

Garlic should be avoided in gastroesophageal reflux disease and peptic ulcer disease. High doses should be avoided in pregnancy. Garlic does pass into breast milk but so far has not been shown to be harmful. Cases of botulism have been reported from chopped garlic or garlic oil left out for long periods at room temperature. Administration of garlic with anticoagulant and antiplatelet drugs should be avoided because of the risk of bleeding.

Conclusion

Fresh garlic may have some cardiovascular benefits, but it is unclear whether it lowers blood lipids or blood pressure as much as originally thought. Aged preparations and cooked garlic are likely to be less effective despite being better tolerated.

Ginkgo Biloba Leaf Extract

Ginkgo, or maidenhair tree (*Ginkgo biloba*), is thought to be the most ancient of living tree species, and it is

now also one of the top selling herbs in Europe and the United States because of its reputed ability to improve cognitive function. *Ginkgo leaf extract* is prepared from ginkgo leaf by a complex process that removes toxic *ginkgolic acid.* This reduces the risk of allergic reactions to the leaves if they are consumed directly. Ginkgo leaf extract contains *24% flavone glycosides* (including the antioxidant *rutin,* which improves capillary fragility) and *6% terpene lactones.*

Mechanism of Action

Ginkgo leaf extract appears to act primarily as a mild *cerebral vasodilator* that increases cerebral blood flow and reduces blood viscosity. *Ginkgolides* inhibit platelet activating factor, and this may improve microcirculatory blood flow in atherosclerotic disease with slightly increased risk of bleeding. There appears to be an antioxidant effect that may be neuroprotective. Although some studies suggested a monoamine oxidase inhibitor (MAOI) effect, this is considered to have questionable clinical relevance.

Indications

Ginkgo leaf extract is most popular for cognitive disorders, including memory loss, dementia, and cerebrovascular insufficiency. A number of well-designed clinical trials have shown modest benefit in Alzheimer's disease, with ginkgo extract appearing as effective as second-generation cholinesterase inhibitors. At least one large (214 patient) study, however, failed to show a memory improvement in dementia patients. Studies are now under way to see whether ginkgo use will protect against development of Alzheimer's disease.

Intermittent claudication appears to benefit from ginkgo therapy: many studies demonstrate improved walking distance and decreased pain. One meta-analysis of eight studies documented statistically significant improvement but questioned its clinical relevance. In some studies, the high doses (240 mg) appeared more effective.

Vertigo and *tinnitus* are difficult to treat conditions for which ginkgo is frequently recommended. At least two trials support the use of gingko extract for vertigo, but the evidence for tinnitus remains inconclusive.

Other suggested uses include sexual dysfunction secondary to selective serotonin reuptake inhibitors (SSRIs), macular degeneration, premenstrual syndrome, and the prevention of acute mountain sickness at high altitude. Some of these uses are supported only by a single study.

Adverse reactions, Contraindications, and Interactions

Allergic reactions are a significant concern with unprocessed ginkgo leaf (ginkgolic acid) but are much less likely to occur with the leaf extract. The malodorous ginkgo fruit cross-reacts with poison ivy (urushiol) and may cause an identical contact dermatitis.

Children eating large numbers (>50) of the uncooked ginkgo kernels have had seizures, and consequently there is some concern about using high doses of ginkgo in seizure patients. However, most patients tolerate gingko extract very well, with only occasional GI upset or headache being reported, and the product is considered safe for healthy nonpregnant adults.

Bleeding complications are an infrequent but serious concern, with subdural hematomas, subarachnoid hemorrhages, hyphema (bleeding of the iris), and surgical bleeding occasionally reported. Stopping ginkgo administration prior to surgery and the avoidance of its use with anticoagulant drugs and perhaps with aspirin is recommended. Use of ginkgo extract should be *avoided in pregnant women and children,* since at least one study showed in a ginkgo preparation small amounts of colchicine, a compound that can block cellular division and cause abortion; however, it is unclear whether this is a problem in all ginkgo preparations.

Ginkgo may reduce the effectiveness of *thiazide diuretics* for blood pressure control and at least theoretically should be avoided with MAOIs. There is also a suggestion that ginkgo may decrease male and female fertility, and it should be avoided in those trying to conceive.

Dose

For cognitive function, total daily doses of 120 to 240 mg divided into 2 or 3 doses of ginkgo leaf extract are recommended. For intermittent claudication, 240 mg a day would be preferable.

Conclusion

The preponderance of evidence indicates that ginkgo is an effective mild cerebral and perhaps general vasodilator that may mitigate cognitive decline in the elderly. Its effect on memory in younger adults is less clear; although some studies show a benefit, others do not. Ginkgo should be avoided with anticoagulants and used with caution with antiplatelet medication. Although ginkgo's effectiveness in intermittent claudication, vertigo, SSRI-induced sexual dysfunction, acute mountain sickness, and other indications may not yet be well enough established for widespread clinical use, this ancient herb may still play a role in 21st-century medicine.

Ginseng

Panax ginseng describes the root from two species of plants, *Asian* ginseng (*Panax ginseng*) and *American* ginseng (*Panax quinquefolius*), popularly used for improving stamina and providing a sense of well-being. The

terms red and white ginseng refer to how the root is processed, not the species of origin. *Red* ginseng roots are steam-cured prior to drying, while *white* ginseng is bleached and dried. Panax ginsengs contain triterpenoid saponins called *ginsenosides* (also called *panaxosides*), of which up to 18 types are recognized as having differing and sometimes opposing pharmacological properties.

Siberian ginseng (*Eleutherococcus senticosus*) should not be confused with Panax ginseng. Although it belongs to the same plant family (Araliaceae), it is a much larger, more abundant, and consequently less expensive plant. Like Panax ginseng, however, it is used as a tonic and adaptogen, a nonmedical term meaning that it helps the body adapt to stress in a variety of ways. Siberian ginseng does contain saponins (*eleutherosides*) but no ginsenosides. To date, in spite of its popularity, there is little conclusive evidence of clinical efficacy.

Mechanism of Action

Ginsenosides are thought to be the active principles in Panax ginseng root. The various subtypes can have opposing pharmacological actions: Rg1 stimulates the central nervous system (CNS) and elevates blood pressure, while Rb1 does just the opposite. Somehow these multiple ginsenoside constituents are thought to act in concert to provide increased stamina. In addition, these compounds have antiplatelet aggregation effects and antioxidant properties, and they may stimulate the immune system.

Indications

Despite the long popularity of ginseng and its evident mild stimulatory effect, there is less conclusive evidence for its clinical effectiveness than for many of the other herbs discussed in this chapter. In regard to improving cognitive function, most studies have failed to prove a consistent benefit. A recent investigation of ginseng's effect on physical stamina found that an 8-week course of therapy failed to improve aerobic *work capacity.* Ginseng has been studied as a diabetic agent, with reduced hemoglobin A1c levels and improved glucose control being documented in a small trial. Although there is some intriguing work with ginseng as a cancer preventive, there is not enough evidence to suggest its clinical use at this time.

Adverse Reactions, Contraindications, and Interactions

Ginseng is generally considered safe for nonpregnant healthy adults; however, at sufficient doses, ginseng may elevate blood pressure and cause insomnia, palpitations, nervousness, and tremor in susceptible individuals. These effects are increased if caffeine or other stimulants are taken concurrently. Both Panax and Siberian ginsengs should definitely be avoided in any patient with poorly controlled hypertension. Dizziness, headache, diarrhea, and nausea have also been reported. A controversial *ginseng abuse syndrome* consisting of tremor, elevated blood pressure, insomnia, and anxiety may also occur.

Diabetic patients have had hypoglycemia on ginseng, so sugars must be monitored, and insulin or other hypoglycemic medication dosages may have to be reduced. The use of ginseng with anticoagulants (e.g., warfarin) and antiplatelet drugs is to be avoided because of the theoretical risk of increased bleeding. Also, coadministration of ginseng with digoxin and MAOIs should be avoided.

Dose

Capsules of powdered root (100, 250, and 500 mg) are available, and doses range from *200 to 600 mg per day.* Ginseng may also be taken as a tea or extract. A 3-*month maximum* treatment course followed by a 2-week break between courses has been recommended. A major concern is that many commercial preparations do not contain the quantity of herb stated on the label. In one assessment of 54 tested ginseng products, 60% showed subtherapeutic amounts of active ingredients, and 25% showed no evidence of any ginseng at all.

Conclusion

Ginseng has been popular for more than 2000 years as a tonic for improved stamina and sense of well-being, particularly in the elderly. Although subjective quality of life reports substantiate this tradition, objective evidence of improved cognitive function and physical stamina remains incomplete or lacking. Further studies of standardized ginseng preparations will be necessary to clarify its use in fatigue and diabetes.

Kava

Kava-kava (*Piper methysticum*) is a South Pacific island shrub the rhizome or root of which was used in the past as a ceremonial beverage and that today is popular as an *anxiolytic.* Historically, women prepared the kava by pounding and then chewing it. After being allowed to ferment in bowls, the kava was drunk by male islanders to mark a special event. The herb would induce a pleasant euphoric tranquility and contribute to the group's social cohesion. The active ingredients are thought to be *kavapyrones* (also known as kavalactones), a family of related synergistically active compounds that include *kawain* and *methysticin.*

Mechanism of Action

The exact mechanism of action is unclear, but it is thought that kavapyrones may act in the amygdala, producing a tranquilizing and muscle relaxant effect.

Despite inducing mild sedation and euphoria, there is usually no cognitive or memory impairment at typical doses. Chewing the root results in a *local anesthetic* effect with temporary numbness. High doses may cause gait impairment, dilated pupils, and eventually impaired motor performance.

Indications

Kava may be effective for the short-term treatment of anxiety. A number of small trials have shown extracts, standardized to 70% kavapyrones, to be significantly and consistently more effective than placebo. Additional studies suggest that kava acts centrally as a *muscle relaxant* and likely has *neuroprotective* and nonopioid *analgesic* properties.

Adverse Reactions, Contraindications, and Interactions

Although kava was considered relatively safe until recently, GI upset, headache, allergic skin reactions, elevated liver function tests, and rare extrapyramidal reactions may occur. It should be avoided in patients with known liver disease. Slowed reflexes and diminished judgment may occur at high doses. Heavy chronic use may produce a psychological (rather than physiological) *habituation* and a pellagralike skin condition known as *kava dermatitis* characterized by reddened eyes and dry flaking skin with a yellow discoloration; flavokawains A and B are yellow pigments isolated from kava and are likely causative. Despite the resemblance to pellagra, niacin does not reverse this condition.

Heavy kava users have also been observed to lose weight and have low plasma protein levels and low platelet and lymphocyte counts. Pulmonary hypertension and shortness of breath have rarely occurred. Kava should be avoided in pregnant women and children, since the consequences of use are unknown. A recent cause for concern is an uncommon idiosyncratic liver toxicity associated with kava use; in some cases, this has been severe enough to warrant liver transplantation. It is unclear whether kava alone is to blame, but the safety of this herb is under review. Several European countries, where this problem was first reported, have either suspended sales or are acting to make kava a prescription drug.

Kava should not be used with alcohol, benzodiazepines, barbiturates or other sedatives because of their additive effects. In one case, coma resulted from mixing alprazolam and kava. Patients have complained that kava, while relaxing the body, may be less effective for mental anxiety with obsessive or racing thoughts than are the benzodiazepines.

Dosage

Kava preparations are frequently *standardized to 30 to 70% kavapyrones.* Doses of *100 mg* (*70% kavapyrones*) *three times daily* are often used for anxiety. Kava is sometimes drunk as a tea (2–4 g of root placed in 150 mL of hot water followed by straining). Treatment may take several weeks to be fully effective, but should be *limited to no more than 3 months* of drug administration.

Conclusion

Kava appears to act somewhat like an *herbal tranquilizer* to produce a calm, relaxed state, often with mild euphoria. At recommended doses it has little effect on cognitive performance. Although it is safe for most adults, prolonged or excessive use may create psychological dependency and health problems.

Milk Thistle

Milk thistle (*Silybum* [*Carduus*] *marianus*) is a spiny European plant with white-veined leaves and milky sap, the seed of which is used to treat liver disease. Milk thistle *seed extract* is used orally in the treatment of *alcoholic and other cirrhoses* and in Europe intravenously for its *hepatoprotective effect in Amanita and other mushroom poisonings.* It is grown in this country primarily as a "*liver cleanser*" and is reputed to protect this organ from a wide array of toxins. Milk thistle seed contains the active principle *silymarin,* a complex of flavonolignan compounds including silibinin (silybin), silidianin, and silychristin.

Mechanism of Action

Silymarin is thought to protect the liver by *preventing the entry of toxins* into the hepatocyte and by stimulating *nucleolar polymerase A,* which, in turn, increases protein synthesis and liver regeneration. Silymarin undergoes enterohepatic circulation, increasing its concentration in hepatocytes. It is also an *antioxidant* in its own right and is considered to have some cytoprotective effect against carcinogens.

Indications

Alcoholic cirrhosis has been improved (faster return of liver enzymes to baseline) in at least three trials, although one multicenter Spanish study failed to demonstrate any change in the clinical course. There is no evidence to support the use of milk thistle to increase alcohol tolerance, although it is certainly being used for this purpose. The effectiveness of silymarin for *viral hepatitis* is not clear, although several trials demonstrated enough benefit to encourage further studies.

Intravenous silymarin has been demonstrated to lower mortality from *Amanita mushroom poisonings,* but this formulation is available only in Europe. Animal studies have demonstrated hepatic protection against alcohol, acetaminophen, and mushroom toxins and protection against hepatic fibrosis with bile duct occlusion. There is also evidence of silybin protecting against cisplatin-induced *nephrotoxicity* in rats. It is not yet clear whether milk thistle extract offers any renal protection to humans.

Adverse Reactions, Contraindications, and Interactions

Milk thistle appears to be remarkably safe, with *loose stools* due to increased bile solubility and occasional *allergic reactions* being the common side effects. It has not been evaluated in children or in pregnant women. There are no known serious drug or herb interactions.

Dosage

Dry extract capsules standardized to *70% silymarin* (*calculated as silibinin*) are administered at 200 to 400 mg/day or 12 to 15 g of dried seed per day. Teas are not recommended, since silymarin is not water soluble.

Conclusion

Milk thistle has shown promise in improving liver function parameters in various hepatotoxic situations, such as alcoholic cirrhosis and mushroom poisoning. It is still unclear whether it will offer protection against viral hepatitis and various nephrotoxic agents.

Saw Palmetto

Saw palmetto (*Serenoa repens*) is a dwarf American palm native to the extreme southeastern United States. A lipidosterolic extract of its berries contains fatty acids (especially lauric acid), phytosterols, monocylglycerides, and polysaccharides. Fatty acids constitute more than 80% of the extract and are thought to be the most clinically effective component. It is widely used to treat *benign prostatic hypertrophy* (*BPH*). The berries themselves are less well absorbed than the extract and are therefore believed to be less effective.

Mechanism of Action

Saw palmetto extract can *inhibit the enzyme 5-α-reductase in vitro.* This enzyme converts testosterone into *dihydrotestosterone* (*DHT*), which in turn contributes to prostatic enlargement. Saw palmetto also appears to have an *antiinflammatory effect* and can reduce *DHT binding* to prostatic androgen receptors (*antiandrogenic effect*). Despite its proposed 5-α-reductase mechanism, saw palmetto has not consistently lowered serum testosterone, DHT, or *prostate-specific antigen* (*PSA*) levels, so it is likely that other mechanisms exist. While several earlier studies did indicate lowered PSA levels, more recent research has not supported these findings. It appears that saw palmetto does not shrink the total prostate either, although it may reduce the size of the transition zone or inner prostatic epithelium.

Indication

Numerous (but not all) trials have indicated improvement in *BPH symptom scores* compared to placebo with 1 to 3 months of therapy. Saw palmetto extract appears to be equally effective as finasteride (see Chapter 63) but is less effective than α_1-adrenoceptor antagonists. No information appears to be available on the use of saw palmetto in the prevention of hair loss.

Adverse Reactions, Contraindications, and Interactions

Headache and GI symptoms are the most frequently reported side effects. It is possible to reduce GI side effects, such as nausea, abdominal discomfort, and diarrhea, by taking the extract with food. Theoretically, decreased libido or erectile dysfunction could also occur. Because of saw palmetto's possible hormonal effects (and lack of indications for use), pregnant and nursing women should avoid it. It is important to rule out prostate cancer in those taking saw palmetto for BPH, since the symptoms are similar. The effect of saw palmetto on prostatic cancer would likely be beneficial but not curative. No drug interactions have been reported.

Dose

For BPH, 320 mg of the lipidosterolic extract by mouth daily in two divided doses with food is usually recommended. It must be taken for a *minimum of 3 months* and perhaps indefinitely. The dried berries and tea are not recommended, since the fatty acids responsible for clinical effect would be largely lost.

Conclusion

Saw palmetto extract is a fairly well tolerated, safe alternative to finasteride for *long-term treatment of BPH,* although α_1-adrenoceptor blocking agents undoubtedly afford more rapid symptom relief.

St. John's Wort

St. John's wort (*Hypericum perforatum*) is a yellow-flowered perennial European herb that has become widely naturalized in the United States. Its name is

derived from the Old English word for plant, *wort,* and from the fact that it often starts blooming around June 24, St. John's day. Although St. John's wort has traditionally been used for wound healing, insomnia, rheumatism, and depression, it is most popular today for the treatment of mild to moderate depression.

The leafy parts of the herb contain naphthodianthrones (e.g., *hypericin*), flavonoids (e.g., *quercetin*), and phloroglucinols (e.g., *hypaphorine*). Although this herb is now commonly *standardized for its hypericin content,* it appears that its other constituents may also be just as pharmacologically active.

Mechanism of Action

Just how St. John's wort treats depression is not clearly understood. It is possible that this herb's various components may work synergistically rather than through a single active substance, mimicking the action of traditional antidepressants. High concentrations can affect in vitro *serotonin reuptake,* but it is unclear whether this would occur in a patient taking standard oral doses. The hypaphorine constituent may possess serotonin reuptake inhibitor activity, and it also inhibits synaptic uptake of γ amino butyric acid (GABA) and L-glutamate. Earlier studies demonstrated some monoamine oxidase inhibition, but this action now seems unlikely to be clinically relevant. Flavonoid components and hypericin also may weakly inhibit catechol-*O*-methyl-transferase (COMT). *Melatonin,* surprisingly, has also been identified in St. John's wort and may play a role in its sleep-enhancing and antidepressant effects.

Indications

St. John's wort is very popular as a physician-prescribed antidepressant in Europe and is widely used for this purpose—usually without medical guidance—in the United States. A meta-analysis of 23 studies concluded that St. John's wort was more effective than placebo in treating mild to moderate depression and was as effective as imipramine and standard antidepressants. It was also better tolerated than the antidepressants to which it was compared. A recent meta-analysis, however, *failed to find St. John's wort effective for severe depression.*

Adverse Reactions, Contraindications, and Interactions

St. John's wort is usually well tolerated, but insomnia, dizziness, fatigue, restlessness, GI upset, constipation, dry mouth, and allergy are reported as possible side effects. Hypomania has also been reported in several cases, and rarely, photosensitivity can be a problem following high doses; hypericin seems to be the component responsible for the photosensitivity. Sun-induced neuropathy has also been described, and it is possible that hypericin may also increase the risk of cataracts with prolonged use. While a prior allergy to the herb is the main contraindication, St. John's wort should also be avoided in pregnant and breast-feeding women (it may increase uterine tone) and in children until its safety is further established.

A major emerging concern in St. John's wort use is the numerous clinically significant herb–drug interactions that have been reported. St. John's wort appears to be a major inducer of the cytochrome *P450 3A4* (*CYP3A4*) *enzyme system* in the liver. This first came to light following acute heart transplant rejection in a person taking *cyclosporin* and St. John's wort. The cyclosporin levels remained subtherapeutic until St. John's wort was discontinued. A similar phenomenon was noted with AIDS patients taking *protease inhibitors* and *nonnucleoside reverse transcriptase inhibitors* (*NNRTIs*). Concomitant use of St. John's wort reduced the effectiveness of these medicines as well. Since then, St. John's wort has been shown to reduce plasma levels of *digoxin, warfarin, theophylline,* and *oral contraceptives.* Breakthrough bleeding has been observed in young women taking this herb, and patients starting oral contraceptives should be counseled to use backup contraception if they take St. John's wort or antibiotics. St. John's wort can adversely affect many other common medications, including *nonsedating antihistamines, antifungals, chemotherapeutic agents,* and *calcium channel blockers.*

SSRIs should not be taken with St. John's wort because of the risk of the onset of a *serotonin syndrome* characterized by nausea, tremor, and weakness. Alcohol also should be avoided. St. John's wort can increase *opioid*-induced sleep.

Dose

St. John's wort is commonly used at 300 mg of extract (standardized to 0.3% hypericin) three times daily for 6 weeks or longer. Short-term treatment is usually ineffective.

Conclusion

St. John's wort is probably effective for mild to moderate but not severe depression. Although well tolerated in most patients, a major concern is its numerous herb–drug interactions mediated by its induction of the cytochrome P450 enzyme system.

Soy and Other Phytoestrogens

Soybeans (*Glycine max*) are protein-rich legumes widely grown around the world as a food crop. They are the major dietary source of *isoflavones,* which are broken down in the intestine into the phytoestrogens *genis-*

tein and *daidzein.* It is believed that the lower risk of breast cancer, cardiovascular disease, and osteoporosis in Asian women is partly due to their high soy diet, since these benefits are lost when they adopt Western dietary habits. Flaxseed, from flax (*Linum usitatissimum*), is the source of another type of phytoestrogen, *lignan,* as well as linolenic acid and omega-3 fatty acids. Red clover (*Trifolium pratense*) contains *isoflavones* as well as *coumarin* and produces effects somewhat similar to those of diethylstilbestrol. The negative effect of red clover on sheep fertility threatened the economy in New Zealand at one time.

Perhaps the most marketed herbal phytoestrogen is black cohosh, or black snakeroot (*Cimicifuga racemosa*), a tall woodland perennial with white torchlike flowers native to eastern North America. The rhizome contains *triterpene glycosides* and many other ingredients that appear to have phytoestrogenic effects. Other traditional herbs sometimes promoted as phytoestrogens, such as dong quai (*Angelica sinensis*), have little medical evidence to support their use.

Mechanism of Action

Soy isoflavones appear to act as *selective estrogen receptor modulators* in that they can occupy and block the β-estrogen receptor. In premenopausal women with normal estrogen levels, soy therefore would have an overall antiestrogen (estrogen blocking) effect, whereas in postmenopausal women lacking estrogen, a weak estrogenic effect would be observed. Soy may also increase the excretion of bile acids and lower cholesterol.

The mechanism of black cohosh's phytoestrogen effect is unclear, although it may also inhibit estradiol binding to estrogen receptors. It does not appear to contain isoflavones like soy, and there are conflicting findings on its estrogenic activity. Early reports of luteinizing hormone suppression have been contradicted by more recent research showing no change in gonadotropins or estradiol. There appears to be no stimulatory effect on estrogen receptor–positive breast cancer cells.

Indications

Soy is possibly effective in reducing menopausal symptoms, such as hot flashes, although it is much less effective than estrogens for this purpose. Higher isoflavone doses than are typically achieved in the U. S. diet are necessary to protect against osteoporosis. High isoflavone soy protein intake outperformed lower isoflavone supplements in this regard. *Ipriflavone,* a semisynthetic isoflavone, is effective in the treatment and prevention of osteoporosis and is used for this purpose in Europe and Japan. In the United States, the FDA has approved the use of soy in conjunction with a low-fat diet for cholesterol reduction. There also is evidence that diets high in soy protein reduce the likelihood of prostate cancer. There is much less evidence available regarding the effectiveness of red clover and flaxseed; however, they too appear to hold some promise for menopausal symptoms, lipid reduction, and prostate cancer.

Black cohosh (*Remifemin* preparation) appears modestly effective in menopausal symptom relief, according to several German studies of up to 6 months' duration; however, more research is necessary before it can be recommended as an estrogen alternative. Black cohosh is less effective than estrogen for symptom reduction and is not known to have any effect against osteoporosis.

Adverse Reactions, Contraindications, and Interactions

While soy is generally considered safe, it may induce *nausea, bloating,* and *allergic reactions* (itchy rashes or even asthma if inhaled as dust) in some people. One study suggested that high midlife soy (tofu) consumption may be associated with *cognitive decline* in later life. However, educational and social differences between the high- and low-tofu groups may also account for some of these findings. Research findings in regard to the safety of soy in breast cancer patients conflict, with an in vitro study suggesting possible stimulation of estrogen-dependent breast cell cultures.

Black cohosh may cause nausea, vomiting, hypotension, and even miscarriage. It is absolutely contraindicated in pregnancy. Red clover contains coumarins and should therefore be avoided with anticoagulants. Diets high in red clover isoflavones have reduced livestock fertility and theoretically could do the same in humans. *Flaxseed may cause nausea, diarrhea, and flatulence.* Cyanogenic nitrates in flax (especially in immature seed pods) have produced toxic reactions.

Dose

Soy protein doses of 20 to 60 g daily are used to reduce hot flashes and to lower elevated cholesterol. Higher doses of isoflavones (2.25 mg/g soy protein) or more than 60 g soy protein may help prevent osteoporosis.

Black cohosh root doses vary widely, with up to 2000 mg/day of root being taken several times daily. *Remifemin* is the best-studied brand, and tablets containing 40 mg of black cohosh extract with 1 mg of triterpenes are given as one or two tablets twice daily.

Conclusions

Soy appears to have weak estrogenic activity when taken after menopause but may block the effects of more potent estrogens (thereby reducing breast cancer risk) when used before menopause. It can reduce menopausal symptoms but is less effective than estrogen in this regard. Although long-term high soy diets

may help prevent osteoporosis, it is likely that most U. S. women will not consume enough to be adequate for osteoporosis treatment. Semisynthetic or concentrated isoflavone preparations may play a role in the future.

Black cohosh may reduce menopausal symptoms, and it appears safe and well tolerated for at least a 6-month period. It lacks the other proven benefits of estrogen, however. There is less information to recommend red clover and flaxseed, although they remain widely used for this purpose.

A listing of other popular herbs and their proposed actions is given in Table 69.4.

TABLE 69.4 Other Popular Herbs and Their Chief Indications

Herb	Principal Indication
Aloe vera	Topical use for burns and skin irritation
Bearberry (*Uva ursi*)	Urinary tract infections
Bilberry	Visual and circulatory problems
Boldo	Digestive disorders
Butcher's broom (Ruscus)	Vein disorders
Cascara sagrada	Laxative
Cat's-claw	Inflammatory conditions (little evidence)
Chamomile	Digestive disorders, antispasmodic
Chaste tree	Menstrual disorders
Dong quai (*Angelica sinensis*)	Gynecological disorders (little evidence)
Evening Primrose	Eczema, mastalgia
Ginger	Motion sickness, Antiemetic
Golden seal	Anti-infective (toxic at higher doses)
Gotu kola (Indian pennywort)	Mental fatigue
Green tea	Antioxidant (cancer and heart disease prevention)
Hawthorn	Mild heart failure, BP reduction
Horse chestnut seed	Varicose veins
Licorice	Demulcent, peptic ulcer (high doses elevate BP)
Mistletoe	Anticancer agent (scant evidence, potential toxicity)
Pau d'arco	Multiple chronic conditions (scant evidence)
Senna	Laxative
Skullcap	Immune system support
Slippery elm	Demulcent, coughs
Tea tree oil (Melaleuca)	Skin infections
Turmeric	Antioxidant, antiinflammatory
Valerian	Sleep disorders
Wild yam (Dioscorea)	Menopause symptoms; does not supply progesterone

Study Questions

1. Which herb is most frequently used to treat migraine headache?
(A) Kava
(B) Hawthorn
(C) Feverfew
(D) Ginseng
(E) Garlic

2. Which herb is most frequently used to treat benign prostatic hyperplasia?
(A) Green tea
(B) Bilberry
(C) Cayenne
(D) Ginseng
(E) Saw palmetto

3. Which herb is most frequently used to treat anxiety?
(A) Garlic
(B) Saw palmetto
(C) Ginkgo
(D) Kava
(E) Echinacea

4. Select the herb most frequently used to treat fatigue.
(A) Ginseng
(B) Uva ursi
(C) Horse chestnut
(D) Evening primrose
(E) Golden seal

5. Your 80-year-old patient complains of forgetfulness and frequent ringing in his ears (tinnitus) and vertigo. He has seen an ear, nose, and throat specialist, but his examination produced normal findings, and he was told that the problem would probably wax and wane in severity. An extensive neurological evaluation and head computed tomography scan also produced normal findings. What herb might be beneficial for his condition?
   (A) Garlic
   (B) Peppermint
   (C) Ginkgo
   (D) Ginger
   (E) Valerian
6. Before giving permission for the patient in question 5 to take this herb, you forgot to ask about his other medications. Which one of the following drugs could present a problem if taken concomitantly?
   (A) Coumadin
   (B) Propranolol
   (C) Lisinopril
   (D) Acetaminophen
   (E) Amlodipine
7. Which one of the following statements is true regarding St. John's wort?
   (A) It may produce photosensitivity at low doses.
   (B) It may induce the cytochrome P450 system.
   (C) It may be unsafe when high tyramine foods are ingested.
   (D) It may increase the levels of many commonly prescribed medications.
8. Which one of the following statements is true of the Chinese herb ma huang (*Ephedra sinensis*)?
   (A) *Ephedra* has been associated with increased risk of hypertension and tachycardia but not stroke.
   (B) The FDA recommends that it be taken for no more than 1 month.
   (C) The FDA recommends that ephedra alkaloids be limited to no more than 8 mg per dose.
   (D) Ephedra is dangerous at any dose and has no legitimate role in herbal medicine.

ANSWERS

1. **C.** Feverfew has several studies supporting its effectiveness as a prophylactic agent for migraine headache. Kava is best known for its antianxiety effects, hawthorn for its use in congestive heart failure, and ginseng as a tonic to increase energy levels. Garlic is used for a variety of conditions, including hyperlipidemia and hypertension.
2. **E.** Saw palmetto reduces the symptoms of prostatic obstruction with long-term use and appears to be as effective as finasteride. Green tea is recommended as an antioxidant and for its reputed cardiovascular benefits. Bilberry is used for improving night vision, while cayenne pepper is applied topically as a counterirritant for neuralgia. Ginseng is commonly used to boost energy and stamina.
3. **D.** Kava is often recommended for anxiety, and it appears significantly more effective than placebo for this condition. Garlic is used for cardiovascular benefits, saw palmetto for prostatic hypertrophy, and ginkgo as a cerebral vasodilator. Echinacea is considered an immunomodulating herb with potential benefit in viral illnesses.
4. **A.** Ginseng is used to increase energy levels and induce a general sense of physical and mental well-being. Bearberry or uva ursi is a natural treatment for urinary tract infections, whereas golden seal is taken as a general anti-infective. Horse chestnut is used in the management of varicosities. Evening primrose oil (linoleic acid) is commonly thought of as a treatment for either eczema or mastalgia.
5. **C.** Ginkgo would be the most likely herbal treatment to benefit this patient, since it would improve cerebrovascular blood flow and cognitive function. Vertigo and tinnitus may also respond, although there is more evidence for the former. Garlic is traditionally used for cardiovascular benefits (lipid, blood pressure reduction), but it would be unlikely to produce immediate results. Peppermint is used as an antispasmodic in irritable bowel syndrome, while ginger tea is a common carminative (gas reducer) and motion sickness treatment. Valerian is useful as a sedative.
6. **A.** Coumadin, taken in conjunction with ginkgo, could increase the risk of bleeding. Ginkgo has an antiplatelet effect, which has produced bleeding complications in this clinical setting. The other medications listed are not known to have this problem. Acetaminophen, unlike aspirin, does not have an antiplatelet effect.
7. **B.** St. John's wort significantly induces the cytochrome P450 system. St. John's wort has numerous herb–drug interactions thought to be caused by this mechanism, which speeds the elimination of many medications and results in subtherapeutic (not higher) drug levels. Photosensitivity may be associated with high doses but is unlikely to be caused by average or low doses of this herb. St. John's wort does interact with selective serotonin reuptake inhibitors and MAO inhibitors. However, it is not thought necessary to avoid tyramine while taking St. John's wort because it is no longer thought to have clinically significant MAO activity.
8. **C.** The FDA now recommends that for safety reasons, ephedra should be limited to 8 mg or less per single dose and that a total daily dose of 24 mg not be exceeded. These are much lower than past dosage recommendations. The new recommendations also suggest a 1-week (not 1 month) limitation of treatment. Stroke is certainly a possible complication.

Despite many concerns about unsupervised use of ephedra, it may still have a useful role when used in healthy patients at proper doses.

SUPPLEMENTAL READING

Blumenthal M, Goldberg A, and Brinckmann J. (eds.). Herbal Medicine: Expanded Commission E Monographs. Newton, MA: Integrative Medicine Communications, 2000.

Cupp MJ. (ed.). Toxicology and Clinical Pharmacology of Herbal Products. Totowa, NJ: Humana, 2000.

Fetrow CW and Avila JR (eds.). Professional's Handbook of Complementary and Alternative Medicines. Springhouse, PA: Springhouse, 1999.

Jellin JM et al. Pharmacist's Letter/Prescriber's Letter Natural Medicines Comprehensive Database (3rd ed.). Stockton, CA: Therapeutic Research Faculty, 2000.

CASE Study Ma Huang and Athletic Performance

A 20-year-old student athlete went to a university health service with supraventricular tachycardia (heart rate above 200), dizziness, weakness, nausea, tremor, and diaphoresis. He denied any history of heart arrhythmias, and medical history was unremarkable save for penicillin allergy. Family history was negative for heart disease. The patient said he took no medications except creatine for weight lifting. His alcohol intake was limited to up to a six-pack of beer on weekends and he denied both smoking and drug abuse. On further questioning, the patient reluctantly admitted drinking an orange-flavored beverage that had been spiked with ma huang (*Ephedra sinica*) to enhance his performance prior to a weightlifting session that afternoon. The symptoms began shortly afterward. He had used this preparation before without becoming ill, but this time he had added an extra scoop "for good measure." The patient was transferred to the emergency department and observed closely until his tachycardia resolved. Explain the causes of the patient's symptoms.

ANSWER: The active ingredient of ma huang is ephedra, an alkaloid whose derivatives (ephedrine, pseudoephedrine) are ingredients in FDA-approved over-the-counter cold and allergy medicines. Although effective and safe at correct dosages in healthy patients, the intake of ephedra compounds became controversial after their widespread use as a stimulant and appetite suppressant ("herbal fen-phen") caused a spate of adverse reactions (>800) along with several fatalities. The FDA has recommended that total ephedra alkaloids in herbal preparations be limited to no more than 8 mg per dose and that no more than 24 mg per 24 hours (rather than previous recommendations) be taken. Therapy should also be limited to only 1 week. Excessive dosages have caused insomnia, nervousness, headaches, tremor, hypertension, seizures, heart attack, stroke, and death. However, in vulnerable patients, life-threatening adverse reactions have occurred with doses as small as 4 to 20 mg/day.

The correct diagnosis was somewhat delayed in this case by the patient's understandable reluctance to confess to ma huang supplementation. Although up to one-third of U. S. patients may be using herbs, few ever inform their health care providers. Frequently patients are reluctant to discuss the use of unauthorized therapies (stimulants, anabolic steroids, illicit drugs, and herbs), especially if they fear a disapproving reaction on the part of their health care provider. This extends to a wide variety of other behaviors as well and can place both the patient and the physician in difficult or dangerous situations. Fortunately, it is possible to counsel patients about the dangers of an herb or drug without condemning them personally. Providers should create a comfortable environment for the patient to share vital information without fear of reprisal or loss of confidentiality. A blanket off-the-cuff rejection of anything the patient values (sexual issues, herbs, dietary supplements) may result in loss of rapport, with the patient likely continuing the behavior in a clandestine manner. The best way to encourage patients to discuss their use of herbs is to ask them about herb use while taking a medical history. Most patients are glad for the opportunity to discuss their herb use once they realize they won't face condemnation.

Patients with cardiovascular disease (including hypertension), diabetes (risk of hyperglycemia), pregnancy (uterine contractions), prostatism, and anxiety disorders are among those who should not take ma huang at any dose. Drug–herb interactions occur with MAOIs (hypertensive crisis), phenothiazines (tachycardia, hypotension), β-blockers (hypertension) and theophylline (increased CNS effects). Of course, caffeine and other stimulants have an additive effect.

CASE Study Phytoestrogens and Menopause

A 55-year-old postmenopausal patient returns to the clinic 6 months after being prescribed *Premarin* and *Provera* for hot flashes, vaginal dryness, insomnia, and mood swings. She took hormone replacement therapy (HRT) for 2 months and had significant relief of symptoms. Even so, she noted breast tenderness on this regimen that worried her despite her recent negative mammogram report. When she read in an article that long-term estrogen (>5 years) might increase her risk of breast cancer by up to 30%, she abruptly stopped therapy. Despite the return of her earlier symptoms, she adamantly refused further HRT even when informed again of its effectiveness for osteoporosis. However, she was very interested in pursuing dietary therapy with phytoestrogens, since this is what several women in her church group are doing.

This patient asks how much soy and what type of soy products she must eat to get relief. She questions whether soy phytoestrogens will do "all of the good things and none of the bad," as she has been told. She asks about the safety and effectiveness of other phytoestrogens and about any other "natural" estrogen alternatives to conjugated equine estrogens.

ANSWER: In spite of the many benefits of HRT, about 80% of prescriptions for it are never filled or are discontinued. Many physicians are frustrated when they discover their patients have stopped therapy without their input, more often than not because of fear of breast cancer. Other commonly cited side effects include weight gain, bloating, and spotting. It appears that the tide of public and possibly even scientific opinion may be turning against estrogen therapy. The Heart and Estrogen/Progesterone Replacement Study trial has demonstrated a possible increase in cardiac events in the first 2 years of therapy, although subsequent cardiac risk appears to decline. Overall there was no benefit in reducing risk of death from chronic heart disease in women at risk. Other trials, including the Nurse's Health Trial, suggest that HRT can be associated with a significant (up to 30%) increase in breast cancer after 5 or more years of use, and more than 10 years of HRT has been associated with increased mortality from ovarian cancer. Finally, the recent National Institute of Health trial demonstrating increased breast cancer and cardiovascular risk associated with HRT has altered professional practice as well as public perception of estrogen's risk.

Phytoestrogen dietary therapy has become increasingly attractive to women in the present climate of care. These substances are not estrogens at all, but they bind to estrogen receptors and may act like selective estrogen receptor modulators. Many plant sources of phytoestrogens were found, including soybeans, other legumes, and flaxseed. Soybeans are among the best sources of the isoflavones genistein and daidzein. Soy may now be consumed in a variety of ways: fresh, frozen, dried, roasted (soy nuts), tofu (soybean curd), tempeh (fermented soybeans and grains), soy milk, soy flour, miso (fermented soy paste), and textured vegetable protein. Some soy products may have lost their isoflavone content in processing: soy cheese, soy oil, and tofu yogurt. Flaxseed contains another type of phytoestrogen, lignans, as well as omega-3 fatty acids. About 1 tablespoon of flaxseed could be considered equivalent to one serving (50 g) of soy, and flaxseed may be an alternative for those who dislike tofu.

Although there is some controversy about how much soy must be consumed to benefit from its phytoestrogen effect, it is believed that two servings per day will modestly reduce menopausal symptoms and the risk of breast cancer. More than three servings may reduce cholesterol. Although it has yet to be proved that dietary soy will stop osteoporosis, a synthetic isoflavone, ipriflavone, has been used in Japan and Europe to treat osteoporosis. Large doses of soy (6–8 servings per day) are believed by some to help this condition as well.

Phytoestrogens appear to reduce the risk of breast cancer, because their estrogenic effect is actually quite weak (one two-hundredth of estradiol) and yet by occupying estrogen receptors, they protect the breasts from more potent estrogens. In an estrogen-deficient postmenopausal patient, they provide a modest estrogenic effect, while in an estrogen-rich environment they actually protect the breasts from estrogen stimulation. Soy may also block tyrosine kinase, an enzyme necessary for the growth of cancer cells.

Allergies to soy may be a concern for some patients, and there may be a cross-reaction with peanut allergy. Bloating and gas occur, especially in those unaccustomed to soy products.

Some women are rejecting conjugated equine estrogens in favor of preparations containing lower-potency estriol, a weak human estrogen produced in pregnancy and thought to be more protective of the

CASE Study Phytoestrogens and Menopause—cont'd

breast. *Tri-Est,* a human estrogen formulation comprised of 80% estriol, 10% estradiol, and 10% estrone (the latter two to increase potency) and *Bi-est,* composed of 80% estriol and 20% estradiol (some converted to estrone) may be ordered at compounding pharmacies. Usual doses of both are 2.5 to 5 mg per day. Many other women elect to take phytoestrogenic herbs rather than soy isoflavone dietary supplements. These less well studied herbs include black cohosh (*Remifemin*) and red clover (*Promensil*). The Chinese herb dong quai has not yet been shown to be effective for menopausal symptoms in clinical trials.

It is not yet clear what the ideal postmenopausal regimen is, but certainly the risks of estrogen replacement are becoming more of a concern to physicians and their patients. Phytoestrogens appear to be relatively safe for the breast, but there are legitimate concerns that they will fail to protect women from osteoporosis. In addition, their safety for women with a history of breast cancer is still quite controversial. Although the epidemiological evidence indicates a protective effect against breast cancer, some in vitro studies on soy isoflavones suggest a possible stimulatory effect on estrogen-dependent breast cancer cells. It makes sense to tailor regimens to bone density studies and assessment of breast cancer risk.