

# A Review of 12 Commonly Used Medicinal Herbs

MaryAnn O'Hara, MD, MSt; David Kiefer, MD;  
Kim Farrell, MD; Kathi Kemper, MD, MPH

A large and increasing number of patients use medicinal herbs or seek the advice of their physician regarding their use. More than one third of Americans use herbs for health purposes, yet patients (and physicians) often lack accurate information about the safety and efficacy of herbal remedies. Burgeoning interest in medicinal herbs has increased scientific scrutiny of their therapeutic potential and safety, thereby providing physicians with data to help patients make wise decisions about their use. This article provides a review of the data on 12 of the most commonly used herbs in the United States. In addition, we provide practical information and guidelines for the judicious use of medicinal herbs.

*Arch Fam Med.* 1998;7:523-536

More than one third of Americans use herbs for health purposes, spending over \$3.5 billion annually.<sup>1,2</sup> Yet patients (and physicians) often lack accurate information about the safety and efficacy of herbal remedies. Imagine the following are patients in your primary care practice. How would you advise them?

- Jane, who has chronic hepatitis C and receives medicine for both hypertension and schizophrenia, asks if she can take milk thistle to protect her liver.
- John, who has the human immunodeficiency virus, has an increasing viral load. He expresses fear of "medicine," but requests information about St John's wort (SJW) in hopes of "naturally" curing his human immunodeficiency virus and depression.
- Sam's wife bought him valerian to help him sleep, saw palmetto for his urinary difficulties, and ginkgo to improve his memory. He is inclined to throw the herbs away but wants your opinion.
- After you inform Stephanie that she is 3 months pregnant, she asks what effects the herbs she has taken for months will have on her fetus (ginger for nausea, feverfew for headaches, and pennyroyal to induce a period).

- Your spouse has high cholesterol, your child has recurrent ear infections, and you have trouble relaxing after a hectic day at the clinic. Prompted by your patients' questions, you wonder if any herbal remedies might benefit your family.

Popular use of medicinal herbs makes it necessary for physicians to become aware of their health benefits, risks, and uncertainties so that they can educate their patients about these issues. To assist clinicians in this task, this article reviews existing data on the history, safety, and efficacy of 12 of the most commonly used and best-studied medicinal herbs (**Table 1**). In addition, it summarizes general information about herbal therapies, including an overview of regulatory history (**Table 2**), important similarities and differences between medications approved by the Food and Drug Administration (FDA) and herbal therapies (**Table 3**), and the nature of available data about medicinal herbs. Finally, lists of reliable introductory resources (**Table 4**) and guidelines for patients (**Table 5**) are provided.

## A HISTORICAL PERSPECTIVE

Plants have been used medicinally throughout history. Through the first half of this cen-

From the Robert Wood Johnson Clinical Scholars Program, University of Washington Health Sciences Center (Dr O'Hara), and the University of Washington Family Medicine Network, Swedish Family Medicine Residency (Drs Kiefer and Farrell), Seattle; and the Center for Holistic Pediatric Education and Research, The Children's Hospital, Boston, Mass (Dr Kemper).

This article is also available on our Web site: [www.ama-assn.org/family](http://www.ama-assn.org/family).

**Table 1. Twelve Common Medicinal Herbs\***

Herb Scientific Name Part Used	Common Uses (Type of Evidence/ Recommendation)†	Safety‡§	Dose¶	Cost**
Chamomile <i>Matricaria recutita</i> , <i>Chamaemelum nobile</i> Flower	Mild sedative (III-C) Mild spasmolytic (III-B) Vulnerary (wound healing), (II.3-B)	GRAS†† Rare allergic reaction and contact irritation. Avoid ocular preparations	Tea as necessary Compress as necessary	\$0.10 per tea bag
Echinacea <i>Echinacea purpurea</i> , <i>Echinacea</i> <i>angustifolia</i> Leaf, stalk, root	URI treatment (I-B) URI prevention (I-C) Vulnerary (wound healing), (III-C) Immune stimulation (III-C) Antimicrobial (HIV), (IV-C [D])	No serious side effects known Historically misidentified and contaminated Long-term use may be immunosuppressive	Not standardized Dried extract: 300-400 mg tid Tincture: 30-50 drops (1 drop = 20 µL) tid	\$0.25-\$4 per day
Feverfew <i>Tanacetum</i> <i>parthenium</i> Leaf	Headache prophylaxis (I-B) Rheumatoid arthritis (I-E)	5%-15% oral or GI irritation Rebound headaches possible Avoid in pregnancy (traditional menses inducer) May potentiate platelet inhibitors	25-75 mg (1-3 leaves) bid, standardized to 0.2% parthenolide	\$0.10-\$0.50 per day
Garlic <i>Allium sativum</i> Cloves, root	≥9% ↓ lipids (LDL, TG), (I-B) Mild antihypertensive (I-B) Antiplatelet (II.1-B) Antioxidant (I-B) Antimicrobial (bacteria, fungus, and viruses [HIV]), (III, IV-C [D]) Cancer prevention (II.3-D) and treatment (III-D)	GRAS, including in pregnancy, lactation, and childhood No serious side effects known Mild side effects: halitosis, body odor, topical irritation, allergy (rare), GI upset May potentiate hypoglycemic and antiplatelet therapy	Fresh cloves: 0.5-1 qd Pills: 600 mg-900 mg qd, standardized to 0.6%-1.3% allicin Powder: 0.4-1.2 g	\$0.04-\$0.70 per day
Ginger <i>Zingiber officinale</i> Root	Antiemetic (I-B) (mildly prophylactic and therapeutic against nausea from motion, chemotherapy, pregnancy, and surgery)	GRAS, including in pregnancy, lactation, and childhood No serious side effects known May inhibit platelet aggregation GI upset (mild) Allergy (rare)	Capsules: 250-1000 mg tid-qid Tea: steep powder or fresh herb	\$0.12 per dose
Ginkgo <i>Ginkgo biloba</i> Leaf	Dementia: slows cognitive deterioration (I-B) Mild effects, similar to tacrine Claudication: 50% ↑ in pain-free walking distance (II.1-B)	No serious side effects known Mild side effects: GI upset, headaches, allergic skin reactions May inhibit platelet aggregation	Use extract standardized to 6% terpenoids, 24% flavonoids 40-80 mg bid-tid	\$0.30-\$1.80 per day
Ginseng <i>Panax ginseng</i> , <i>Panax quinquefolius</i> Root ("Siberian ginseng" is not a true ginseng)	Endurance/adaptation enhancer —Conflicting motor results (C) —↑ Cognitive function (I-C) —Resistance to stress (III-D) —Androgenic and estrogenic (II.2-D) Enhances "quality of life" (II.1-D) Immune/endocrine stimulant (III-D)	GRAS High cost without proven benefit Avoid use with other stimulants and in patients with cardiovascular disease (potential hypertensive and chronotrope) May increase digoxin levels Mastalgia and postmenopausal bleeding (rare) Rare fatalities attributed to contaminants	Root: 1-3g qd Pills: 100-300 mg tid, extract standardized to ≥7% ginsenosides	\$0.30-\$2.00 per day

tury, many herbs were considered conventional medicines and as such were included in medical curricula and formularies (eg, *United States Pharmacopoeia* and *The National Formulary*). Two important factors fostered a schism between mainstream drugs and herbal therapies in the United States: the development of a pharmaceutical industry capable of mass-producing purified chemicals, and regulatory changes by the FDA.

In 1962, thalidomide was found to be teratogenic and Congress passed an amendment to the Food and Drug Act to increase assurance of drug safety and efficacy. While successful in general, the amendment initiated a regulatory dilemma regarding herbal therapies in the United States (Table 2). No longer can substances

be considered drugs based on traditional use alone. A would-be manufacturer must gain FDA approval; the profit to be made from a patented product is the motivating factor. Traditional herbal therapies cannot be patented, and therefore lack sponsors for the costly (\$230 million) and lengthy (8-10 years)<sup>3</sup> approval process. By default, many medicinal herbs are not legally considered drugs and are not regulated as such by the FDA. The FDA suggests but cannot require that manufacturers of herbal therapies provide customers with scientific data in support of advertising claims. Furthermore, the FDA must prove that an herbal product is unsafe or ineffective before it can require the product to be removed from the market.

#### HERBS AND FDA-APPROVED MEDICATIONS: SIMILARITIES AND DIFFERENCES

Patients are often unaware of important similarities and differences between medicinal herbs and FDA-approved medications. For example, some mistakenly think of herbs as "natural" alternatives to chemicals, failing to recognize that herbs are composed of bioactive chemicals, some of which may be toxic (see **Table 6** for a list of commonly used herbs with toxic effects that probably outweigh their potential benefits). Also, patients are often unaware that about 25% of modern pharmaceutical drugs have botanical origins, such as digoxin from foxglove, morphine from pop-

**Table 1. Twelve Common Medicinal Herbs\* (cont)**

Herb Scientific Name Part Used	Common Uses (Type of Evidence/ Recommendation)†	Safety‡§	Dose¶	Cost**
Goldenseal <i>Hydrastis canadensis</i> Root, rhizome	Mask illicit drugs in urine (II.3-E) Berberine constituent effects: Antidiarrheal in children ( <i>Escherichia coli</i> , <i>Giardia</i> , and cholera), (I-B) Antiseptic, topical (III-C)	Generally well tolerated Traditional literature warns that huge (unspecified) doses can cause GI upset, hypertension, cardiac inotropy, seizures, and respiratory failure Avoid in pregnancy (uterotonic) and neonates (causes jaundice) May oppose anticoagulants	Use alternate sources of berberine, 10 mg/kg per day	\$0.45-\$1.25 per dose
Milk thistle <i>Silybum marianum</i> Fruit	Hepatoprotection against: —Acute hepatitis, ie, mushroom poisoning (II.3-B), drugs (III-C) —Chronic active hepatitis (I-B) —Cirrhosis (I-B, conflicting data)	No serious side effects known Rare: diarrhea, allergy	Capsules: 140 mg bid-tid, standardized to 70% silymarin IV silymarin in acute poisoning: 20-50 mg/kg per day	\$0.44-\$2.00 per day (oral)
St John's wort <i>Hypericum perforatum</i> Flower, leaf	Mild-moderate depression (I-B) (long-term use not yet studied) Antimicrobial (HIV), (III-C [D]) Vulnerary (III-C) Neoplastic inhibition (III-D)	Photosensitization is rare, usually in fair-skinned people taking large doses No clinical MAO-inhibition and/or related drug/food interactions Avoid use with other antidepressants	Tablets: 300 mg tid of extract standardized to 0.3% hypericin Topical	\$0.17-\$1.35 per day (oral)
Saw palmetto <i>Serenoa repens</i> Fruit	Benign prostatic hypertrophy (B) —↑ Flow, ↓ frequency, ↓ PVR (No. 7 II-1) —Efficacy = finasteride (I) —↓ Androgen and estrogen prostatic nuclear receptors (I) —5 $\alpha$ reductase inhibition (IV)	Unlike finasteride, not associated with ↓ libido or changes in PSA No serious side effects or drug interactions known Mild, rare effects: GI upset, headaches, diarrhea	Tablets: 320 mg qd of extract standardized to 85%-95% fatty acids and sterols	\$ 0.80-\$1.20 per day
Valerian <i>Valeriana officinalis</i> Root	Somnagogue (sleep aid), (I-B) Spasmolytic (III-C)	GRAS Mild, rare effects: headache, palpitations, insomnia	Capsules: 400 mg qhs as necessary ( $\geq$ 12 years) Tea: 2-3 g = 1 tsp tid Tincture: 3-5 mL tid	\$0.06-\$0.19 per dose

\*GRAS indicates generally recognized as safe; URI, upper respiratory infection; HIV, human immunodeficiency virus; tid, three times daily; GI, gastrointestinal; bid, twice daily; LDL, low-density lipoprotein; TG, triglycerides; qd, every day; qid, four times daily; IV, intravenous; MAO, monoamine oxidase; PVR, post-void residual; PSA, prostate-specific antigen; qhs, every night. See text for more information and references.

†Adapted from study reference system of the US Preventative Services Task Force (USPSTF), 1996, 2nd edition. Type of Evidence: I indicates randomized controlled trial; II, other human study (1 = placebo-controlled trial, 2 = cohort or case-controlled study, 3 = case series); III, animal study (vs expert opinion in USPSTF rating); IV, in vitro studies (not a category in USPSTF). Recommendation: A indicates safe and effective; B, probably safe and effective; C, probably safe, possibly effective; D, insufficient data; and E, unsafe or ineffective.

‡Data are often lacking on drug interactions and effects of long-term use.

§Content and quality of commercial products are not regulated in the United States and can vary considerably.

|| Safety in pregnancy, lactation, and childhood is unknown (and use in these groups therefore not recommended) unless specifically indicated.

¶Patients should use standardized preparations, which are more reliable and cost-effective.

\*\*Range of costs for commercial products ( $\geq$ brands) in typical drug store.

††Generally recognized as safe as a food supplement by the FDA.

pies, aspirin from willow bark, and tamoxifen from the Pacific yew tree.<sup>4</sup>

Unlike the FDA-approved over-the-counter and prescription medications, medicinal herbs are not required to demonstrate either safety or efficacy prior to marketing, nor are they regulated for quality. Nevertheless, herbal therapies are not necessarily less expensive than patented drugs and are rarely covered by medical insurance. In contrast to the purified, standardized, and potent FDA-approved drugs, herbs contain an array of chemicals, the relative concentration of which varies considerably depending on genetics, growing conditions, plant parts used, time of harvesting, preparation, and stor-

age. In addition, herbs may be contaminated or misidentified at any stage from harvesting through packaging.

#### THE NATURE OF EVIDENCE ABOUT MEDICINAL HERBS

Most research on medicinal herbs is conducted in areas of the world where the use of medicinal herbs is mainstream, particularly in Asia and Europe. For the past 3 decades, the German Health Authority has systematically reviewed the evidence on about 300 herbs and formulated clinical guidelines. An English translation of the resulting *German Commission E Monographs* is due for release in 1998.<sup>3</sup> Although argu-

ably the best compendium of clinical information about herbs in the world, it does not disclose the scientific basis for its conclusions. Nevertheless, such guidelines provide hypotheses to prompt quality human trials, optimally with randomized, double-blind, placebo-controlled (RDBPC) trials. Research in the United States will be bolstered by the creation of the Office of Complementary and Alternative Medicine within the National Institutes of Health, Bethesda, Md.

Data about the safety and efficacy of medicinal herbs are limited in a number of ways. In some cases, the best data are years old, limited to in vitro or animal studies, and/or only available in

**Table 2. Genesis of a Regulatory Dilemma: US Legislation on Herbal Remedies**

Year	Act/Agency	Purpose/Details	Effects on the Status of Herbal Therapies
1906	Food and Drug Act	Outlawed misbranding and adulteration	Therapeutic herbs continue to be included in the <i>National Formulary</i> and the <i>United States Pharmacopoeia</i>
1938	Federal Food, Drug and Cosmetic Act	Required safety testing prior to marketing after new elixir killed 105 people	Most traditional remedies with history of safe use are grandfathered in under law
1962	(Kefauver-Harris) Drug Amendments	Required proof of safety and efficacy to be marketed as a drug Considered only evidence presented to expert panels, primarily by companies interested in marketing a patentable (therefore profitable) drug	Most herbs not patentable and therefore Lacked sponsor for costly approval process Never considered for approval, irrespective of efficacy or safety Reassigned status to "foods or food supplements" No longer legally considered medications No longer regulated by Food and Drug Administration (FDA) Subject to confiscation if labeled like a drug, eg, with traditional indications, doses, or cautions
...	FDA GRAS List	FDA maintains a list of substances generally recognized as safe (GRAS)	Includes about 250 herbs based on their use as food additives (eg, garlic and ginger)
1993	FDA Commissioner David Kessler, MD	Proposed removing herbal products from the market given booming market despite unproven safety or efficacy	More protest letters sent to Congress than about any issue since the Vietnam war, fueled by a multimillion-dollar industry campaign
1994	Dietary Supplement Health and Education Act	Shifted burden of proof to FDA (eg, that claims are misleading or an herb is unsafe) Altered restriction on labeling	Ineffective assurance of safety, efficacy, or quality Confusing guidelines about labeling: May state: effect on "structure or function of the body" or "mechanism" or "describe general well-being from consumption of the nutrient" May not state: false or misleading claims, or that the product can treat or prevent any specific disease May be accompanied by: balanced, nonpromotional literature
1997	Federal Commission on Dietary Supplements	Recommended manufacturers provide science-based evidence about product to consumers	Anticipate little effect, as lacks enforcement capability

journals outside the United States. Some clinically important types of information are particularly sparse in the literature, such as the results of negative trials, drug interactions, effects in special populations (eg, children and pregnant or lactating women), and toxic reactions. In some cases, good evidence about short-term side effects comes from well-controlled human trials. However, information about the effects of long-term use is usually based on case reports rather than prospective studies. As noted earlier, traditional use has revealed serious toxic effects associated with some common medicinal herbs (see Table 6). On the other hand, the FDA categorizes about 250 herbs as "generally recognized as safe" (GRAS) for consumption based on long-term and/or widespread traditional use without significant side effects. This article reviews several herbs on the FDA GRAS list, including chamomile, garlic, ginger, ginseng, and valerian. Evidence about the safety and efficacy of these and 7 other commonly used medicinal herbs are reviewed below.

## CHAMOMILE

### *Matricaria recutita*

**Common name:** German chamomile

***Chamaemelum nobile*** (English or Roman chamomile)

**Common uses:** Sedative, spasmolytic, anti-inflammatory, vulnerary (wound healing)

**Investigational uses:** Antioxidant  
**Side effects:** Allergy (rare)

Chamomile is a daisylike, apple-scented flower that has been used medicinally for thousands of years. Anglo-Saxons believed it was 1 of the 9 sacred herbs given to humans by the god Woden. In contemporary Germany, it is considered a cure-all. Chamomile is cultivated worldwide for use as a sedative, spasmolytic, anti-inflammatory, and vulnerary (wound-healing) agent. Few human studies have evaluated these traditional uses.

Only chamomile's vulnerary effects have been studied in a controlled human trial, with incon-

clusive results. A recent RDBPC trial found no difference between chamomile and placebo in preventing mucositis in 164 patients receiving fluorouracil, half of whom used chamomile 3 times daily for 14 days).<sup>6</sup> However, the study was possibly too short to detect a difference, as mucositis is largely a result of immunosuppression, and therefore takes weeks to develop. In another randomized, placebo-controlled trial, radiation-induced skin reactions were less frequent and appeared later in chamomile-treated areas, but the differences were not statistically significant.<sup>7</sup>

Animal studies support chamomile's traditional use as a vulnerary anti-inflammatory, spasmolytic, and anxiolytic agent. The flavonoid component apigenin exhibits dose-dependent, reversible inhibition of irritant-induced skin inflammation<sup>8</sup> and protects against gastric ulcers induced by medications, stress, and alcohol.<sup>9</sup>

**Table 3. Herbs and Food and Drug Administration (FDA)–Approved Drugs: Similarities and Differences**

Factor	Legal Medications (FDA-Approved)	Herbal Therapies
Mechanism	Biochemical	Biochemical
Origins	25% Plant origin	Raw plants
Efficacy	Evidence required, but not always based on well-controlled trials	Proof not required
Safety	Must be well studied, within acceptable limits, and detailed on drug label or insert	Evidence of safety not required and often unavailable
Dose	Established, usually by dose-response studies	Burden of proof with FDA to show herbal therapies unsafe Some guidelines exist, usually based on historical precedent or tradition, occasionally based on dose-response in clinical trials Standardized products are preferential and available for some herbs (eg, garlic, ginkgo, St-John's-wort, saw palmetto, and valerian) Not necessarily standardized by content of active ingredients, which are often unknown
Pharmacokinetics	Usually well characterized	Rarely known
Potency	Standardized	Varies with genetics, growing conditions, time harvested, plant part used, preparation, and storage
Proof of purity	Required	Varies greatly High potential for contamination; history of case reports
Identification	Some confusion possible with coexistence of generic and multiple trade names	Problematic, beginning with misidentification of plants at harvesting Products should be labeled with and chosen by scientific name ( <i>genus species</i> , eg, <i>Echinacea purpurea</i> is the most used and studied <i>Echinacea</i> species—many of its common names are shared by other plants)
Quality control	Required	Not required Improving with self-regulation by herb industry
Cost	Wide range Elevated for patented drugs	Highly variable Extracts are the most concentrated and cost effective
Insurance coverage	Often	Rarely

**Table 4. Introductory References**

**Books**

- Blumenthal M, Gruenwald J, Hall T, Riggins C, Rister R. *German Commission E Monographs: Medicinal Plants for Human Use*. Austin, Tex: American Botanical Council; 1998. English translation in press.
- Duke JA, Emmanus PA. *The Green Pharmacy*. Emmaus, Pa: Trondal Press; 1997.
- Murray M. *The Healing Power of Herbs*. 2nd ed. Rocklin, Calif: Prima Publishing; 1995.
- Tyler VE. *Herbs of Choice: The Therapeutic Use of Phytomedicinals*. Binghamton, NY: Pharmaceutical Products Press; 1994.

**Journals**

- American Botanical Council, Austin, Tex. *HerbalGram*
- Facts and Comparisons, St Louis, Mo. *Lawrence Rev Nat Prod*

**Online**

- The American Botanical Council: <http://www.herbalgram.org>
- The Phytochemical Database: <http://www.ard-grin.gov/nfrlsb/>

Apigenin also binds the same receptors as benzodiazapines; it exerts anxiolytic and mild sedative effects in mice<sup>10</sup> and relaxes intestinal spasms.<sup>11</sup> In vitro, the essential oil acts as an antioxidant<sup>12</sup> and kills some skin pathogens (some *Staphylococcus* and *Candida* species).<sup>13</sup>

Chamomile is considered safe by the FDA, with no known adverse effects in pregnancy, lactation, or childhood. It caused no adverse reactions in the human trials discussed earlier. While chamomile's therapeutic effects and safety

remain to be definitively proven in human trials, its beneficial effects seen in animals and its good safety record in widespread traditional use by humans make it an acceptable home remedy for soothing mild skin irritation, intestinal cramps, or agitated nerves. In the United States, it is commonly consumed as a tea or applied as a compress. Patients with severe allergies to ragweed should be warned about possible cross-reactivity to chamomile and other members of the aster family (eg, echinacea, feverfew, and milk thistle). It

should not be taken in conjunction with other sedatives, such as benzodiazapines or alcohol.

**ECHINACEA**

*Echinacea purpurea*, *Echinacea angustifolia*, and *Echinacea pallida*

**Common name:** Purple coneflower

**Common uses:** Prevention and treatment of colds, wound healing

**Investigational use:** Anticancer

**Side effects:** Possible suppression of immunity with habitual use

Echinacea is a purple coneflower native to North America. Plains Indians valued this member of the daisy (Asteraceae) family for its medicinal properties and introduced it to European settlers. By the 1920s, this acclaimed anti-infectious and vulnerary agent was listed in the *National Formulary* and out-sold all other products of one major pharmaceutical company. Its popularity dwindled after the advent of antibiotics, only to experience a resurgence in recent years. It is the most popular herb in the United States, generating more than \$300 million in sales annually.<sup>1</sup> Three of the 9 species of *Echinacea*

**Table 5. Medicinal Herbs: Patient Information Sheet**

- Plants have been used throughout history to improve health.
- Many modern medicines came from plants. Examples include aspirin (from willow bark), morphine (from poppies), and digoxin (from foxglove). Scientists are still discovering valuable medicines in ancient plants; eg, tamoxifen, which is used to treat breast cancer (from Pacific yew trees).
- Herbs used for health purposes are drugs. They are chemicals that can affect the human body in helpful or harmful ways.
- Plant products are not necessarily safe. Hemlock, for example, was used to kill Socrates. Some commonly used herbal therapies are also unsafe.
- Traditional herbal therapies are not necessarily effective. Only trials in humans comparing the herbal product with a placebo (inert substance) can determine its effectiveness, appropriate dose, and safety.
- Individual reports of benefit from any drug, including herbs, are not reliable evidence. This is because some people will feel better when treated with a medicine they believe will work, whether it does or not.
- Science is not opposed to nature, but rather is a tool to help distinguish natural products that are safe and effective from those that are not.
- Unlike medications approved by the Federal Drug Administration, herbal products
  1. Are not required to prove claims about their safety or effectiveness.
  2. Are not regulated to ensure quality control.
  3. Vary tremendously in concentration of active ingredients and other chemicals.
- If you decide to use herbs for health purposes, the following recommendations can help maximize the potential benefits and minimize the potential risks:
  1. Discuss any drugs you use, including herbal remedies, with your doctor.
  2. If you experience side effects, stop taking the herb and notify your doctor.
  3. Avoid preparations containing more than one herb.
  4. Be wary of commercial claims about herbs; seek unbiased and scientifically based sources of information. Ask your doctor or pharmacist for suggested sources.
  5. Preferentially use products that are standardized to contain a specific amount of active ingredients. Such formulations are generally more reliable, effective, and economical.
  6. Select herbal products carefully. In general, the highest quality products come from Europe or large companies in the United States with national reputations to protect. Only buy brands that list the following information on the package: the herb's common and scientific name, the name and address of the manufacturer, a batch and lot number, an expiration date, dosing guidelines, potential side effects, and details of how quality is ensured.

are used medicinally: *E purpurea*, *E angustifolia*, and *E pallida*. *Echinacea purpurea* is the most commonly used and extensively studied.

In Germany, where most studies have been conducted, echinacea is approved by the Federal Health Agency as supportive therapy for upper respiratory tract infections, urogenital infections, and wounds.<sup>5</sup> In the United States, echinacea is usually marketed alone or in combination with other herbs as a purported immune booster, particularly for the prevention or treatment of colds. Although 26 published controlled trials have evaluated echinacea's therapeutic effects, none is of sufficient methodologic quality to be conclusive.<sup>14</sup> For example, in addition to sharing the flaws of the best studies discussed later, most other controlled trials use formulations of echinacea combined with other herbs. Treatment assignment is neither random nor blind in most studies.<sup>14</sup>

Only 2 RDBPC trials have evaluated *E purpurea*'s effect on

upper respiratory tract infections. In one, echinacea extract demonstrated a statistically significant decrease in symptoms and duration of "flu-like" illness (n = 180).<sup>15</sup> The effects were dose dependent; benefits were noted beginning on day 3 or 4 in patients taking 180 drops (1 drop = 20 µL) of extract daily, whereas volunteers taking 90 drops per day showed no benefit. In the second RDBPC trial with 108 volunteers who had a history of recurrent URIs, prophylactic echinacea extract was associated with less frequent (14% relative risk reduction) and less severe recurrences.<sup>16,17</sup> In some studies, immunocompromised patients seemed to benefit the most.<sup>14</sup> While provocative, interpretation of the results is limited in both of the RDBPC trials by inadequate use or description of the following: diagnostic criteria, randomization process, treatment interventions, methods for assessing outcome, assurance of blinding, detail of results, and quality statistical analysis.<sup>14</sup>

In animal studies, echinacea affects several aspects of the immune system; components of echinacea increase the number of circulating white blood cells,<sup>18</sup> enhance phagocytosis,<sup>19</sup> stimulate cytokine production, and trigger the alternate complement pathway.<sup>20</sup> In vitro, echinacea displays direct bacteriostatic and antiviral activity and stimulates the production of cytokines (interferon, tumor necrosis factor, interleukin 1, and interleukin 6).<sup>3,15</sup> Based on its stimulation of cytokine production, echinacea is being investigated as a possible antineoplastic agent in preliminary human trials.<sup>21</sup>

Topical echinacea exhibits multiple vulnerary mechanisms, including the anti-infective activity noted above, stimulation of fibroblasts, and inhibition of inflammation (metabolism of arachidonate to prostaglandins).<sup>22</sup> In rodents, echinacea also decreases inflammation, protects against radiation-induced skin damage, and hastens wound healing.<sup>23</sup>

Available evidence on echinacea's therapeutic potential is incomplete, but does suggest a possible supportive role in treating infections and wounds. However, well-designed clinical trials are needed to substantiate echinacea's efficacy, clarify appropriate dosages, and confirm safety. Despite the fact that the dosage has not been standardized and that preparations are frequently adulterated, no serious side effects have been reported in more than 2.5 million prescriptions per year in Germany and more than a century of use in the United States.<sup>24</sup> Toxicity studies found no mutagenicity in tissue culture, and no clinical or histologic side effects in rats treated with huge doses of echinacea (5 g/kg intravenously and acutely or 8 g/kg per day orally for 1 month).<sup>24</sup> German guidelines discourage use of echinacea in place of antibiotics or for more than 8 weeks (one study suggests that long-term use may suppress immunity).<sup>5</sup>

## FEVERFEW

### *Tanacetum parthenium*

**Common use:** Migraine prophylactic  
**Investigational use:** Antiarthritic  
**Side effects:** Oral ulcers, rebound headaches, allergic reaction (rare)

Feverfew is a daisylike perennial found commonly in gardens and

**Table 6. Common, Potentially Toxic Herbs\***

Herb (Scientific Name)	Purported Use	Possible Toxic Reaction
Arnica ( <i>Arnica montana</i> )	Anti-inflammatory, analgesic, antiseptic	Ingestion associated with gastrointestinal and muscle damage Safe topically, excepting rare allergic reactions
Belladonna ( <i>Atropa belladonna</i> ), "deadly nightshade"	Relaxant, antiulcer	Central nervous system and respiratory depression; anticholinergic
Chaparral ( <i>Larrea tridentata</i> )	Anticancer	Hepatotoxic, tumor trophic
Coltsfoot ( <i>Tussilago farfara</i> ), "cough wort"	Antitussive, salve	Carcinogenic, hepatotoxic, genotoxic Cardiopulmonary stimulant
Comfrey ( <i>Symphytum</i> )	Healing (wounds, ulcers, cancer)	Carcinogenic, hepatotoxic, genotoxic Excreted in breastmilk
Ephedra (Ma-huang) ( <i>Ephedra sinica</i> )	Anorectic, stimulant, bronchodilator	Potent, highly variable $\alpha$ -1 and $\beta$ receptor stimulation Associated with hypertensive strokes, palpitations, and nerve damage Fatalities reported
European mistletoe ( <i>Viscum album</i> )	Antihypertensive, antitumor	Central nervous system and cardiac toxic reaction Gastrointestinal bleeding
Germander ( <i>Teucrium chamaedrys</i> )	Anorectic	Hepatotoxic
Licorice ( <i>Glycyrrhiza glabra</i> )	Expectorant, antiulcer	High or prolonged doses cause pseudoaldosteronism (saline retention and potassium depletion) Hepatotoxic, carcinogenic
Life root ( <i>Senecio aureus</i> )	Emetic Ease labor	Hepatotoxic, carcinogenic
Pennyroyal ( <i>Hedoma pulegioides</i> ), "squawmint," "mosquito plant"	Menstrual disorders, insect repellent	Hepatotoxic Neurotoxic Teratogenic (acetylcysteine is antidote)
Pokeroot ( <i>Phytolacca</i> )	Tonic, anticancer, anti-inflammatory	Gastrointestinal, neurologic, and hematologic toxic reaction May be fatal in children
Sassafras ( <i>Sassafras albidum</i> )	Stimulant, tonic, antispasmodic, anti-inflammatory	Carcinogenic
Indian snakeroot ( <i>Rauvolfia serpentina</i> )	. . .	Neurotoxic reaction (sedation, depression)
Tea tree oil ( <i>Malaleuca alternifolia</i> )	Antiseptic, salve	Central nervous system toxic reaction if ingested Local irritation
Yohimbe ( <i>Pausinystalia yohimbe</i> )	Impotence	Cardiovascular stimulant, neurotoxic, emetic

\*Select list of herbs most likely to be used by family medicine patients. Adapted from Tyler.<sup>2,4</sup>

along roadsides. The name stems from the Latin *febrifugia*, "fever reducer." The first century Greek physician Dioscorides prescribed feverfew for "all hot inflammations." Also known as "featherfew," its feathery leaves are used commonly to treat arthritis and prevent migraines.<sup>25</sup> While feverfew did not reduce symptoms in a double-blind, placebo-controlled (DBPC) trial among patients with rheumatoid arthritis,<sup>26</sup> it has been shown to prevent migraines in 2 of 3 DBPC trials.

The largest and best DBPC trial was a crossover study in which feverfew use was associated with a 70% reduction in migraine frequency and severity (n = 270).<sup>27</sup> Side effects were less frequent than with placebo. In a trial among feverfew users, subjects randomized to receive a placebo instead of continuing feverfew suffered a significant increase in the frequency and severity of headaches, nausea, and vomiting (n = 20).<sup>28</sup> Based on these trials, Canadian health officials re-

cently approved encapsulated feverfew leaves as an over-the-counter medication for migraine prophylaxis. However, migraines were not prevented in a subsequent randomized controlled trial (RCT) using a different formulation of feverfew (0.35% = 0.5 mg of parthenolide, a suspected active ingredient).<sup>29</sup> This highlights the potential variability of contents and effects of different preparations of the same herb, as well as the inadequacy of standardizing herbs to a single ingredient when other bioactive constituent(s) are not well characterized.

Laboratory evidence indicates that feverfew causes vasodilation and reduces inflammation. Feverfew's constituents inhibit phagocytosis, platelet aggregation, and secretion of inflammatory mediators (arachidonic acid and serotonin).<sup>30</sup> Feverfew is thought to down-regulate cerebrovascular response to biogenic amines, consistent with its ability to prevent but not abort headaches, as

well as the months of use needed for clinical efficacy.<sup>25</sup>

In summary, some feverfew preparations can prevent migraines, with efficacy that compares favorably with  $\beta$ -blockers and valproic acid.<sup>31</sup> However, side effects may limit the use of feverfew, as 5% to 15% of users develop aphthous ulcers and/or gastrointestinal (GI) tract irritation.<sup>25</sup> Sudden discontinuation can precipitate rebound headaches.<sup>28</sup> Long-term safety data are lacking. Feverfew should not be used during pregnancy (historically it has been used to induce menstrual bleeding) or in patients with coagulation problems (feverfew can alter platelet activity<sup>30</sup>). For patients who want to try feverfew, expert herbalists recommend a gradual dose increase up to 125 mg/d orally of encapsulated leaves (2-3 leaves) standardized to contain 0.2% parthenolide. However, according to a 1992 study, none of the commercially available North American preparations contained even half of

the recommended parthenolide concentration.<sup>32</sup>

### GARLIC *Allium sativum*

**Common uses:** Antiatherosclerosis (lipid lowering, antithrombotic, fibrinolytic, antihypertensive)

**Investigational uses:** Anticancer  
**Side effects:** Sulfuric odor, contact irritation (rare)

Garlic's historic and worldwide medicinal use have made it one of the most extensively studied medicinal herbs. Nevertheless, the actual therapeutic benefits of this member of the Liliaceae family is unclear. Louis Pasteur first demonstrated garlic's antiseptic activity.<sup>4</sup> Both animal studies and epidemiological analyses suggest anticancer effects.<sup>33</sup> Most current research, popularity, and controversy relate to garlic's use as a putative antiatherosclerotic agent (via antithrombotic, antiplatelet, antihypertensive, and especially antilipidemic effects).

Mainstream medical interest in garlic's potential lipid-lowering effects was stimulated by 2 meta-analyses of RPC trials that found a 9% to 12% decrease in cholesterol in hyperlipidemic patients after at least 1 month of treatment with 600 to 900 mg/d of garlic tablets.<sup>34,35</sup> However, definitive conclusions were limited by methodologic flaws in the trials analyzed.

Results of subsequent better-designed RPC trials have been mixed, with most (4/7) failing to find a significant change in any lipoprotein component<sup>36-39</sup> These studies explicitly sought to overcome limitations of previous trials, such as by providing dietary stabilization prior to treatment and detailing methods to ensure proper control processes and laboratory standards. However, 3 of the negative trials were relatively small ( $N \leq 28$ ), which in one case yielded a marginal power (80%) to detect the expected 9% reduction in cholesterol.<sup>38</sup> Three RPC trials support the positive findings of the meta-analyses, finding a 6.1% to 11.5% cholesterol reduction in the garlic-treated patients. Similar to previous studies, the lipid reduction was

due to a decrease in low-density lipoprotein (LDL)  $\pm$  decreased triglyceride levels.<sup>40-43</sup>

Of the factors that contribute to the discrepancies in data regarding garlic's antilipidemic effects, 2 are probably most important: publication bias (the preferential publication of trials with positive findings) and methodologic flaws. Both factors tend to overestimate the effect of a treatment. In contrast, excluding patients likely to benefit most (patients with severe hyperlipidemia or high-fat diets) might underestimate garlic's effect.

Blood pressure has been monitored in most recent studies of garlic's antilipidemic effects, showing a decrease (systolic and/or diastolic) in the treatment group of some, but not all, trials. Previously, a number of placebo-controlled trials that focused on the antihypertensive effects of garlic demonstrated a modest (-5% to -7%) effect.<sup>44</sup> Several small, nondefinitive RCTs also corroborate garlic's antiplatelet, antithrombotic, and fibrinolytic activity found in animal and in vitro studies.<sup>45</sup>

Dozens of trials suggest, but have not adequately proven, that garlic can decrease the risk factors for atherosclerosis, particularly hypercholesterolemia. Pending conclusive evidence from additional well-designed and adequately powered studies, it is reasonable for patients to choose to take garlic given that it is safe and generally inexpensive. Garlic is considered safe by the FDA, based on the lack of known serious adverse outcomes despite culinary and medicinal use throughout human history (including daily use by pregnant or lactating women). Malodorous breath and skin can be diminished with enteric-coated tablets or by consuming garlic with protein. Allergies and contact irritation occur rarely. Patients who decide to use garlic medicinally should be aware of a few caveats. The main purported active ingredient, allicin, is degraded by crushing, heat, and acid; thus, efficacy is optimized by consuming raw cloves or enteric-coated tablets. The usual dose is 300 mg, taken 2 to 3 times per day, standardized to

at least 1.3% allicin (equivalent to approximately 3 g or 1 fresh clove daily). Finally, the quality of commercial preparations varies greatly, a problem common to many herbal therapies. In an analysis of supposedly standardized preparations, 93% were found to be so lacking in allicin that they were declared expensive placebos.<sup>4</sup>

### GINGER *Zingiber officinale*

**Common uses:** Antiemetic

**Side effects:** Heartburn, allergic reaction (rare)

Like garlic, ginger has been a popular culinary and medicinal herb for thousands of years. For 2500 years, the Chinese have used this plant as a flavoring agent and antiemetic. Ancient Greeks wrapped ginger in bread and ate it after meals as a digestive aid. Ginger is now cultivated in Asia, Africa, and the Caribbean and is used worldwide as a nausea remedy.

The characteristic odor and flavor of ginger root come from a volatile oil (1%-3% by weight) that is composed of shogaol and gingerols. In laboratory animals, the gingerols have analgesic, sedative, antipyretic, antibacterial, and GI tract motility effects.<sup>46,47</sup>

Ginger reduces nausea, according to some, but not all, controlled human trials. In an RDBPC crossover trial of 30 women suffering from hyperemesis gravidarum, ginger (250 mg 4 times a day) significantly decreased the severity of nausea ( $P = .04$ ).<sup>48</sup> Two RDBPCTs report a significant decrease in perioperative nausea and vomiting in gynecological surgery patients who were given 1 g of ginger before surgery.<sup>49,50</sup> In one, ginger was as effective as metoclopramide in reducing the number of episodes of nausea or emesis.<sup>44</sup> However, in another RDBPCT, ginger was not found to be effective in preventing nausea after laparoscopic gynecologic surgery.<sup>51</sup> Regarding motion sickness, ginger was more effective than dimenhydrinate in one controlled trial,<sup>52</sup> but was not effective in another.<sup>53</sup> Such inconsistency of results is found in studies of conventional antiemetics as well, due in part

to the difficulty in measuring symptoms such as nausea. In addition, the effect of antiemetics is often subtle and difficult to discern unless tested in a homogeneous population with a high prevalence of nausea.

It is reasonable for patients to try ginger to treat nausea, not only because data supports its efficacy, but also because it is inexpensive, readily available, and safe. Like garlic, ginger is not known to cause any serious side effects, despite worldwide culinary and medicinal use of ginger. Only 1 of the above controlled human trials noted any side effect, which, ironically, was GI tract upset. It is on the FDA's GRAS list. The usual adult dose is 250 milligrams (1/4 tsp) to 1 g of powdered root several times per day.

### GINKGO *Ginkgo biloba*

**Common uses:** Intracerebral and peripheral vascular insufficiency (dementia and claudication)

**Investigational uses:** Mountain sickness

**Side effects:** Gastrointestinal tract disturbance, headache, contact dermatitis (each is rare/mild)

One of the oldest surviving tree species, *G biloba* has grown in China for more than 200 million years. For thousands of years, traditional Chinese medicine has used ginkgo to treat brain disorders. In the past 20 years, ginkgo has gained worldwide popularity for similar purposes, supported by evidence of its ability to promote perfusion and inhibit oxidative damage. By 1988, German physicians prescribed a standardized extract of ginkgo (Egb 761, Willmar Schwabe GmbH & Co, Karlsruhe, Germany) more than any other medication.<sup>4</sup> Sales in the United States soared to \$240 million in 1997.<sup>1</sup> In Germany, where most of the research has been conducted, the federal health authorities have concluded that treatment with Egb 761 is safe and effective for peripheral and cerebral circulatory disturbances, including claudication and memory impairment.<sup>5</sup> Numerous European clinical trials report Egb 761's efficacy in diminishing symptoms of cerebrovascular insufficiency.<sup>54,55</sup>

In 1997, the first US-based trial corroborated ginkgo's efficacy in the treatment of dementia. In this year-long, RDBPC, multicenter study, Egb 761 was found to stabilize and in some cases improve cognition and social functioning in patients with mild to moderate dementia (Alzheimer disease or multi-infarct dementia).<sup>56</sup> In another trial, healthy geriatric patients demonstrated better cognitive function after taking Egb 761.<sup>57</sup>

Egb 761 improves perfusion peripherally as well as centrally. More than 15 European studies suggest a reduction of claudication symptoms in patients treated with Egb 761, including a 50% increase in pain-free walking distance.<sup>58</sup> Simultaneous benefits on central and peripheral perfusion are demonstrated in a randomized, placebo-controlled trial among 44 Himalayan climbers.<sup>59</sup> The 22 subjects treated with 160 mg/d of Egb 761 developed significantly fewer cerebral (0% vs 41.9%,  $P < .002$ ) and respiratory symptoms (13.6% vs 81.8%,  $P < .001$ ) of mountain sickness than climbers taking the placebo. Egb 761 also decreased vasomotor disorders of the extremities, measured by plethysmography and symptom scores.

The mechanisms of ginkgo's therapeutic effects are not fully understood. They are attributed in part to synergistic effects of its constituents, particularly the flavonoids, terpenoids, and organic acids. These act to varying degrees as scavengers of free-radicals, chemicals implicated in the pathophysiology of Alzheimer disease.<sup>60,61</sup> They also inhibit platelet activation factor and thereby reduce thrombosis, dilate arteries and capillaries, and block the release of chemotactic and inflammatory mediators from phagocytes.

Ginkgo's antidementia effects are similar to that of the prescription drugs donepezil and tacrine.<sup>62,63</sup> While statistically significant, such modest effects are of uncertain clinical benefit. However, ginkgo may have other advantages, such as improvement of peripheral vascular circulation and tolerance of altitude. In addition, ginkgo's side effects are similar to placebo vs potential hepatotoxic ef-

fects with tacrine. While *G biloba* leaves may cause mild GI tract irritation, no serious adverse effects have been noted in human or animal trials, including no mutagenicity or teratogenicity.<sup>64</sup> In contrast, *G biloba* seeds can cause fatal neurologic and allergic reactions and are not used medicinally.<sup>64</sup> Patients should use the extract studied in all reported clinical trials, Egb 761. The dose is 40 mg 3 times per day or 80 mg twice per day of an extract standardized to 24% flavanoid glycoside and 6% terpenoids. Absorption is unaffected by food intake. The duration of benefit after discontinuation is unknown.<sup>65</sup>

### GINSENG

#### *Panax ginseng*

*Panax quinquefolius* (American ginseng, an endangered species)  
(*Eleutherococcus senticosus*, so-called Siberian ginseng, is not in the *Panax* [true ginseng] genus)

**Common name:** Korean ginseng

**Common uses:** "Tonic," performance enhancer, "adaptogen," anticancer, aphrodisiac

**Investigational uses:** All common uses are as of yet unproven but are under investigation

**Side effects:** Tachycardia, hypertension

Ginseng is one of the most popular and expensive herbs in the world. As in ancient China, ginseng is still widely believed to be a panacea; hence, its genus name *Panax*. The common name ginseng ("man-root") stems from a belief that because this root is humanoid in appearance, it can benefit all aspects of the human body. At least 6 million Americans<sup>66</sup> use the root of this slow-growing perennial. It is considered a tonic or adaptogen that enhances physical performance (including sexual), promotes vitality, and increases resistance to stress and aging. While in vitro and animal studies suggest that it has beneficial effects on immune and endocrine functions, evidence of its effects on humans is limited and contradictory.

One reason for lack of definitive data about ginseng's health effects is the inherent difficulty of quantifying intangible benefits such

as “vitality” and “quality of life.” Nevertheless, a 3-month RCT showed a significant increase in subjective “quality-of-life” scores among ginseng users (n = 625).<sup>67</sup> Some small controlled trials report increased endurance, whereas others do not.<sup>68</sup> In an RDBPCT, college-aged volunteers who took 100 mg of ginseng twice daily for 12 weeks experienced a statistical improvement in the speed at which they were able to perform mathematical calculations, but did not experience improvement in motor function or other cognitive functions; no adverse effects were seen in this study.<sup>69</sup> To our knowledge, no studies compare ginseng’s effect with that of inexpensive, widely available cognitive stimulants such as caffeine, nor has an RCT confirmed aphrodisiac effects in humans. However, ginseng was associated with a significant increase in serum hormones (testosterone, dihydroxytestosterone, follitropin, and lutropin) and in sperm numbers and motility in 46 men with oligospermia.<sup>70</sup> A case-control study suggests an association (but not necessarily a causal relationship) between use of ginseng and lower cancer rates (n = 1987 pairs matched for age, religion, marital status, education, sex, occupation, and smoking status).<sup>71</sup>

In Asian cultures, ginseng is commonly consumed by pregnant women and is given to newborns in hopes of bolstering energy. A case-control study of 88 pairs of women (matched only for age and parity) found a significantly lower rate of pregnancy-induced hypertension, but a 3-fold higher incidence of gestational diabetes among ginseng consumers.<sup>72</sup> We do not recommend ginseng use for pregnant or lactating women or for children until safety and efficacy are proven in randomized controlled trials.

Patients who take ginseng risk paying a high price without proven benefit. Commercial preparations of ginseng cost up to \$20 an ounce and vary tremendously in quality. In one analysis of 54 available ginseng products, 85% were determined “worthless,” containing little or no ginseng.<sup>73</sup> To optimize quality and chance of efficacy, only preparations standardized to ginsenoside content

should be used. Patients should be warned that *E senticosis*, marketed as “Siberian ginseng” for commercial reasons, contains no true ginseng.

Despite extensive use, adverse reactions to ginseng are rare and ginseng is on the FDA’s GRAS list. However, at least 1 fatality has been attributed to contamination of a ginseng product with the potent and unpredictable herbal stimulant ephedra. While clear conclusions about the safety of ginseng cannot be drawn from the uncontrolled 1979 case series that coined the term “ginseng abuse syndrome,”<sup>74</sup> ginseng can act as a mild stimulant and should probably be avoided in association with other stimulants or in patients with cardiovascular disease. Rare endocrinologic effects include mastalgia and postmenopausal bleeding, both of which cease with discontinuation of ginseng.<sup>75</sup>

#### GOLDENSEAL *Hydrastis canadensis*

**Common uses:** Antidiarrheal and antiseptic (berberine component)

**Investigational uses:** Antineoplastic and anti-human immunodeficiency virus (berberine component)

**Side effects (large doses):** Mucocutaneous irritation, GI tract upset, cardiac and uterine contractility, vasoconstriction, central nervous system stimulation, neonatal jaundice (displaces bilirubin).

Cherokee Indians introduced this member of the buttercup family to European settlers. It is used topically for eye or skin irritation, and orally for infections. A recent surge in goldenseal’s popularity stems from the erroneous but widespread belief that it can mask illicit drugs in urine toxicology screens. It is also a popular but unproven cold remedy. However, one of its main bioactive constituents, berberine, is an effective antidiarrheal agent.

In one RCT, a single 400-mg dose of berberine sulfate significantly reduced stool volumes and duration of diarrhea among patients with enterotoxigenic *Escherichia coli* and *Vibrio cholerae*.<sup>76</sup> In another controlled trial, berberine (5 mg/kg × 6 days) was more effective

than placebo and as effective as metronidazole (10 mg/kg × 6 days) in treating children with giardia.<sup>77</sup>

Berberine is thought to act intraluminally, as it is poorly absorbed and there is no clinical evidence for systemic anti-infective activity.<sup>78</sup> In vitro studies reveal possible mechanisms of berberine’s antidiarrheal effects. Berberine exerts antimicrobial activity against numerous bacteria, fungi, and protozoa.<sup>79</sup> In addition, it blocks adhesion of bacteria to epithelial cells,<sup>80</sup> inhibits the intestinal secretory response of cholera and *E coli* toxins, and normalizes mucosal histology following cholera toxin damage.<sup>81</sup>

Despite the antidiarrheal efficacy of the chemical berberine, we do not recommend the use of the herb goldenseal for this purpose, both because of this plant’s endangered status and due to the possible toxicity of its other components. For example, traditional herbal literature warns that large (unspecified) amounts of goldenseal (particularly the alkaloid hydrastine) can cause mucosal irritation, GI tract upset, uterine contractions, neonatal jaundice, hypertension, seizures, inotropic cardiac effects, and respiratory failure.<sup>82</sup> It may oppose heparin or coumadin anticoagulation.<sup>83</sup> Goldenseal should not be used by pregnant or lactating women, neonates, or patients with cardiovascular disease, epilepsy, or coagulation problems. No significant side effects have been noted in clinical or animal studies of purified berberine.

#### MILK THISTLE *Silybum marianum*

**Common names:** “Holy Thistle,” “St Mary’s Thistle”

**Common uses:** Hepatoprotectant, antioxidant

**Investigational uses:** Antihyperglycemic

**Side effects:** None known

For more than 2000 years, the seeds of this prickly leaved, purple-flowered plant have been used to treat liver disorders. In addition, all parts of this Kashmir native have been consumed historically as vegetables without report of toxic effects. Silymarin protects against a variety of hepatotoxic agents and

processes in animal experiments. Evidence of its effects in humans is provocative but preliminary.

The best human data deal with silymarin's effect on cirrhosis, with conflicting results from 2 RDBPC trials.<sup>84,85</sup> In the first, the 4-year mortality rate decreased by 30% in patients treated for 2 years with 140 mg of silymarin 3 times a day. Effects were greatest in alcohol-related cirrhosis. In contrast, a recent multicenter RDBPC trial in 200 patients with alcoholic cirrhosis found no differences in progression of disease or mortality after 2 years of treatment with 150 mg of silymarin 3 times per day.<sup>85</sup> Interestingly, glycemic control was significantly improved (lower fasting blood glucose, glycosylated hemoglobins, and insulin requirements) in a randomized, placebo-controlled trial of 60 patients taking silymarin for alcoholic cirrhosis.<sup>86</sup> In another RCT of patients with chronic active hepatitis, 1 week of therapy with oral silymarin (240 mg/d) resulted in decreased serum transaminases and bilirubin values.<sup>87</sup> European physicians routinely treat hepatotoxic mushroom poisoning with intravenous silymarin (20-50 mg/kg per day), decreasing mortality rates by more than half in several case series.<sup>88</sup>

In animal studies, silymarin protects liver cells against a variety of hepatotoxins, including drugs (acetaminophen, amitriptyline, and erythromycin),<sup>89,90</sup> toxins (a-amanitin from deathcap mushrooms, alcohol, and carbon tetrachloride),<sup>91</sup> hemosiderin,<sup>92</sup> viruses, and radiation.<sup>88</sup> Silymarin scavenges free radicals, blocks toxin entry into cells by competing for receptor sites, inhibits inflammation, and stimulates liver regeneration. As a result, it lowers serum transaminase levels, maintains coagulation factor production, and limits necrosis.<sup>88-91</sup> It also prevents renal toxic reactions from cisplatin.<sup>93</sup>

Milk thistle warrants further investigation as a hepatoprotective and regenerative agent. No adverse effects have been reported. Diabetic patients taking silymarin should carefully monitor their blood glucose and may require reduction in standard antihyperglycemic agents to avoid hypoglycemia.<sup>86</sup> The com-

mon dose is a 140-mg capsule, standardized to 70% silymarin, 2 to 3 times a day. A high first-pass effect concentrates silymarin in the liver. Silymarin is poorly absorbed, so concentrated products (ie, extracts) are optimal.

### ST JOHN'S WORT *Hypericum perforatum*

**Common use:** Antidepressant

**Investigational uses:** Anticancer, antiviral (including human immunodeficiency virus)

**Side effects:** Photosensitivity (rare, with large doses)

This 5-petalled yellow flower grows wild in much of the world. While reduced to 1% of its original population in the Pacific United States by ranchers who consider it a bothersome weed, in Europe it is highly valued as an antidepressant. St John's wort is by far the most common antidepressant used in Germany, where physicians prescribe it 4 times more often as fluoxetine hydrochloride.<sup>94</sup> Sales in the United States increased 20-fold between 1995 and 1997, from \$10 million to \$200 million annually.<sup>1</sup> St John's wort has been used for thousands of years for a myriad of conditions. It is named after St John the Baptist because it blooms around his feast day (June 24) and exudes a red color symbolic of his blood. Its scientific name derives from the Greek *hyper* and *eikon*, "to overcome an apparition," relating to ancient belief in its ability to ward off evil spirits. The vulnerary and neurologic effects of this herb were described by Galen, were repeated throughout the Middle Ages and by early American herbalists, and were recently supported by many clinical trials.

A 1996 meta-analysis of 23 randomized, controlled clinical trials of SJW concluded that it is significantly more effective than placebo in treating mild to moderate depression.<sup>95</sup> The 8 studies that compared *H perforatum* with low-dose tricyclics suggested equivalent efficacy, with significantly fewer side effects. The authors noted the need for further studies to determine optimal dosing, long-term side effects, efficacy in maintenance therapy, and relative safety

and efficacy compared with other antidepressants.<sup>95</sup> In response, the Office of Complementary and Alternative Medicine of the National Institutes of Health and the National Institute of Mental Health recently allocated \$4.3 million for the first clinical trial in the United States to address these issues. The 3-year multicenter trial beginning in 1998 will compare SJW with both placebo and fluoxetine hydrochloride.

The mechanism of SJW's antidepressant effects is only partially known. Some in vitro studies demonstrated monoamine oxidase inhibition, but only at concentrations unattainable in vivo.<sup>96</sup> Furthermore, SJW is used extensively (66 million doses in 1994 in Germany) without restriction of tyramine-containing foods and without reported side effects related to monoamine oxidase inhibition. Hypericin is the putative active ingredient. It has a high affinity for  $\gamma$ -aminobutyric acid, the stimulation of which is known to have antidepressant effects.<sup>87</sup> Other studies indicate that hypericin activates dopamine receptors but inhibits serotonin receptor expression.<sup>97</sup> Altered receptor regulation is consistent with the several-week lag between drug initiation and clinical efficacy, similar to other antidepressants.

In addition to SJW's antidepressant effects, evidence beyond the scope of this article supports its historical anti-inflammatory, anti-infective, and vulnerary external applications.<sup>96</sup> Antineoplastic and antiviral applications are experimental.

Existing data on the therapeutic effects of SJW are provocative. However, well-designed clinical trials are needed to determine long-term safety and therapeutic guidelines for use of SJW for different depressive disorders. Prior to the availability of such information, patients who choose to use SJW should use the regimen shown to be effective in the above clinical trials: 300 mg 3 times a day of an extract standardized to 0.3% hypericin. St John's wort is generally well tolerated, but can cause photosensitivity, especially in fair-skinned persons taking large doses. It should not be used during pregnancy (uterotonic) or with other psychoactive agents.

## SAW PALMETTO *Serenoa repens*

**Common uses:** Benign prostatic hypertrophy (BPH), prostatitis

**Side effects:** Gastrointestinal tract upset, headache (each is rare and mild)

Extracts from the fruit of this short, scrubby palm have been used historically to treat urogenital problems. Many modern clinical trials corroborate the ability of saw palmetto extract (SPE) to improve the signs and symptoms of BPH, for which it is a first-line treatment in much of Europe.<sup>98</sup>

Seven of the 8 DBPC trials that have evaluated SPE's efficacy in treating BPH demonstrate significant objective and subjective improvement in BPH symptoms in patients taking 320 mg of SPE for 1 to 3 months.<sup>98,99</sup> However, only 2 of these trials are randomized, and their results conflict. In the shorter randomized trial, SPE is no better than placebo in treating BPH (n = 70 treated for 1 month).<sup>100</sup> In the larger, randomized, multicenter trial (n = 176 treated for 2 months), and in the other 6 DBPC trials, SPE significantly increases urinary flow, decreases nocturia, and decreases postvoid residual.<sup>101</sup> Saw palmetto extract worked as well as finasteride in a randomized, 6-month study of 1098 men, with similar significant improvements in the International Prostate Symptom Score, quality of life, and peak urinary flow rate.<sup>102</sup> Unlike finasteride, SPE did not cause impotence, decrease libido, or alter prostate-specific antigen levels.

A mechanism of SPE's effect on BPH is demonstrated in an RDBPCT in which use of SPE for 3 months results in a significant decrease in prostatic nuclear androgen and estrogen receptors.<sup>103</sup> Prostate size decreased on serial ultrasounds in an open study of 505 men with BPH.<sup>104</sup>

Like finasteride, SPE inhibits the enzyme 5 $\alpha$ -reductase (in vitro), blocking the conversion of testosterone to dihydroxytestosterone, a major growth stimulator of the prostate gland.<sup>105</sup> Saw palmetto extract also blocks the uptake of testosterone and dihydroxytestosterone by the prostate without affecting serum testosterone levels.<sup>105</sup> In addition, its anti-

inflammatory activity (inhibition of cyclooxygenase and 5-lipoxygenase pathways) are thought to be important in decreasing the edematous component of BPH and prostatitis.<sup>4</sup>

These studies support the use of SPE for BPH and show that its efficacy is comparable to that of the 5 $\alpha$ -reductase inhibitor finasteride with significantly fewer side effects. However,  $\alpha$ 1 antagonists are more effective than both SPE<sup>106</sup> and finasteride.<sup>107</sup> The usual dose of SPE is 160 mg twice daily of an extract standardized to contain 85% to 95% fatty acids and sterols. Side effects are rare (<3%) and include mild headaches and GI tract upset.<sup>4</sup>

## VALERIAN *Valeriana officinalis*

**Common uses:** Sleep-aid, anxiolytic, antispasmodic

**Side effects:** Headaches (rare), heart palpitations (rare), insomnia (rare)

The malodorous root of valerian, a pink-flowered perennial that grows wild in temperate areas of the Americas and Eurasia, has been a popular calming and sleep-promoting agent for centuries. German health officials have approved valerian for use as a mild sedative and sleep aid, based on several European clinical trials that demonstrate these effects.

In 2 randomized, blind, and placebo-controlled crossover trials (n = 27 and n = 128), valerian (400-450 mg before bedtime) resulted in significantly improved sleep quality and decreased sleep latency, with no residual sedation in the morning.<sup>108,109</sup> In vitro, constituents of valerian mediate the release of  $\gamma$ -aminobutyric acid<sup>110</sup> and bind the same receptors as benzodiazepines, but with less affinity and milder clinical effects.<sup>111</sup> Habituation or addiction have not been reported.

In the United States, valerian is approved for use in flavoring foods and beverages such as root beer. No serious side effects have been reported. However, a small percentage of consumers experience paradoxical stimulation, including restlessness and palpitations, particularly with long-term use.<sup>112</sup> Some components display cytotoxic and

mutagenic activity in vitro. Although these effects have not been reproduced in vivo even at high doses (1350 mg/kg), valerian probably should not be used by pregnant women. Valerian should not be taken with other sedatives or before driving or in other situations when alertness is required.

## CONCLUSIONS

Physicians need to know about medicinal herbs because many patients use them and are often guided by misconceptions or inaccurate information. Whether or not physicians intend to prescribe herbal therapies, it is important that they understand the potential associated health consequences so that they can help patients make informed decisions about their use. This review aimed to familiarize clinicians with available evidence on 12 commonly used herbs, as well as to indicate areas in need of further research. Popular interest in herbal therapies is stimulating research that will help clarify issues such as the indications, effective doses, and safety of common medicinal herbs.

For patients who choose to use herbal therapies, several guidelines can help them to do so most safely and effectively (Table 5). Patients need to understand that medicinal herbs are drugs, and as such not only have potential benefits, but also the potential to interact with other drugs and to cause toxic reactions. Patients should be informed about important similarities and differences between FDA-approved drugs and herbal remedies, particularly that the herbs are not required to be proven either safe or effective prior to marketing (Table 3). Given the variable purity, potency, and quality of herbal products, they must be selected with care. In general, the best products are from Europe, where quality control regulations exist. In the United States, large stores with national reputations to protect have particular incentive to ensure quality. Finally, patients should preferably use standardized products and consult reputable sources for information about appropriate indications, contraindications, and dosing (see Tables 4 through 6).

Accepted for publication May 1, 1998.

Thanks to the following for their thoughtful comments and assistance: Lisa Butters, Maureen Brown, MD, Chris Vincent, MD, and the Swedish Medical Center Library staff.

Corresponding author: MaryAnn O'Hara, MD, Robert Wood Johnson Clinical Scholars Program, University of Washington Health Sciences Center, 1959 NE Pacific, Room H-220, Box 357183, Seattle, WA 98195 (e-mail: maryanno@u.washington.edu).

## REFERENCES

- Canedy D. Real medicine or medicine show? growth of herbal sales raises issues about value. *New York Times*. July 23, 1998:C1.
- Tyler VE. What pharmacists should know about herbal remedies. *J Am Pharm Assoc*. 1996;36:29-37.
- Murray M. *The Healing Power of Herbs*. 2nd ed. Rocklin, Calif: Prima Publishing; 1995.
- Tyler VE. *Herbs of Choice. The Therapeutic Use of Phytomedicinals*. Binghamton, NY: Haworth Press Inc; 1994.
- Blumenthal M, Gruenwald J, Hall T, Riggins C, Rister R. *German Commission E Monographs: Medicinal Plants for Human Use*. Austin, Tex: American Botanical Council; 1998. In press.
- Fidler P, Lorinzi C, O'Fallon J, et al. Prospective evaluation of chamomile mouthwash for the prevention of 5-FU-induced oral mucositis. *Cancer*. 1996;77:522-525.
- Maiche A, Grohn P, Maki-Hokkonen H. Effect of chamomile cream and almond ointment on acute radiation skin reaction. *Acta Oncol*. 1991;30:395-396.
- Gerritsen M, Carley W, Ranges G, et al. Flavonoids inhibit cytokine-induced endothelial cell adhesion protein gene expression. *Am J Pathol*. 1995;147:278-292.
- Szelenyi I, Isaac O, Theimer K. Pharmacological experiments with compounds of chamomile: experimental studies of the ulcerprotective effect of chamomile. *Planta Med*. 1979;35:218-227.
- Viola H, Wasowski C, Levi de Stein M, et al. Apigenin, a component of *Matricaria recutita* flowers, is a central benzodiazepine receptor-ligand with anxiolytic effects. *Planta Med*. 1995;61:213-216.
- Foster H, Niklas H, Lutz S. Antispasmodic effects of some medicinal plants. *Planta Med*. 1980;40:309-319.
- Rekka E, Kourounakis A, Kourounakis P. Investigation of chamazulene on lipid peroxidation and free radical processes. *Res Commun Mol Pathol Pharmacol*. 1996;92:361-364.
- Aggag M, Yousef R. Study of antimicrobial activity of chamomile oil. *Planta Med*. 1972;22:140-144.
- Melchart D, Linde K, Worku F, Bauer R, Wagner H. Immunomodulation with *Echinacea*: a systematic review of controlled clinical trials. *Phytotherapy*. 1994;1:245-254.
- Braunig B, Dorn M, Limburg E, Knick E. Enhancement of resistance in common cold by *Echinacea purpurea*. *Z Phytother*. 1992;13:7-13.
- Hobbs C. *Echinacea*: a literature review; botany, history, chemistry, pharmacology, toxicology, and clinical uses. *HerbalGram*. 1994;30:33-47.
- Schoneberger D. Influence of the immunostimulating effects of the pressed juice of *Echinacea purpurea* on the duration and intensity of the common cold: results of a double-blind clinical trial. *Forum Immunol*. 1992;2:18-22.
- Bauer V, Jurcik K, Puhlmann J, Wagner V. Immunologic in vivo and in vitro examinations of *Echinacea* extracts. *Arzneim Forsch*. 1988;38:276-281.
- Roesler J, Steinmuller C, Kiderlen A, Emmendorffer A, Wagner H, Lohmann-Matthes M. Application of purified polysaccharides from cell cultures of the plant *Echinacea purpurea* to test subjects mediates activation of the phagocyte system. *Int J Immunopharmacol*. 1991;13:931-941.
- Luettig B, Steinmuller C, Gifford G, Wagner-Matthes M. Macrophage activation by the polysaccharide arabinogalactan isolated from plant cell cultures of *Echinacea purpurea*. *J Natl Cancer Inst*. 1989;81:669-675.
- Lersch C, Seuner M, Bauer A, Siemens M, Hart R, Drescher M. Nonspecific immunostimulation with low doses of cyclophosphamide (LDCY), thymostimulin, and *Echinacea purpurea* extracts (Echinacin) in patients with far-advanced colorectal cancers: preliminary results. *Cancer Invest*. 1992;10:343-348.
- Muller-Jacki B, Breu WPA, Redl K, Greger H, Bauer R. In vitro inhibition of cyclooxygenase and 5-lipoxygenase by alkaloids from *Echinacea* and *Achillea* species. *Planta Medica*. 1994;60:37-40.
- Tubaro A, Traghi E, Del Negro P, Galli C, Della Loggia R. Anti-inflammatory activity of a polysaccharide fraction of *Echinacea angustifolia*. *J Pharmacol*. 1987;39:567-569.
- Mengs U, Clare C, Pooley J. Toxicity of *Echinacea purpurea*: acute, subacute and genotoxicity studies. *Arzneim Forsch*. 1991;41:1076-1081.
- Hobbs C. Feverfew: a review. *HerbalGram*. 1989;20:2636.
- Patrick M, Heptinstall S, Doherty M. Feverfew in rheumatoid arthritis: a double blind, placebo controlled study. *Ann Rheum Dis*. 1989;48:547-549.
- Murphy J, Heptinstall S, Doherty M, Mitchell J. Randomized double-blind, placebo-controlled trial of feverfew in migraine prevention. *Lancet*. 1988;2:189-192.
- Johnson E, Kadam N, Hylands D, Hylands P. Efficacy of feverfew as prophylactic treatment of migraine. *BMJ*. 1985;291:569-573.
- de Weerd C, Bootsma H, Hendricks H. Herbal medicines in migraine prevention: randomized double-blind, placebo-controlled crossover trial of a feverfew preparation. *Phytotherapy*. 1996;3:225-230.
- Heptinstall S, White A, Willimson L, Mitchell J. Extracts of feverfew inhibit granule secretion in blood platelets and polymorphonuclear leukocytes. *Lancet*. 1985;1:1071-1074.
- Welch K. Drug therapy in migraine. *N Engl J Med*. 1993;329:1476-1483.
- Heptinstall S, Awang D, Dawson B, Kindack D, Knight D, May J. Parthenolide content and bioactivity of feverfew: estimation of commercial and authenticated feverfew products. *J Pharm Pharmacol*. 1992;44:391-395.
- Dorant E, van den Brandt P, Goldbohm R, Hermus R, Sturmans F. Garlic and its significance for the prevention of cancer: a critical review. *Br J Cancer*. 1993;67:424-429.
- Warshafshy S, Kamer R, Sivak S. Effect of garlic on total serum cholesterol. *Ann Intern Med*. 1993;119:599-605.
- Silgay C, Neil A. Garlic as a lipid-lowering agent: a meta-analysis. *J R Coll Physicians London*. 1994;28:2-8.
- Simons LA, Galaubramaniam S, von Konigsmark M, Parfitt A, Simons J, Peters W. On the effect of garlic on plasma lipids and lipoproteins in mild hypercholesterolaemia. *Atherosclerosis*. 1995;113:219-225.
- Neil HAW, Silgay CA, Lancaster T, et al. Garlic powder in the treatment of moderate hyperlipidaemia: a controlled trial and meta-analysis. *J R Coll Physicians London*. 1996;30:329-334.
- Isaacsohn JL, Moser M, Stein EA, et al. Garlic powder and plasma lipids and lipoproteins: a multicenter, randomized, placebo-controlled trial. *Arch Intern Med*. 1998;158:1189-1194.
- Berthold HK, Sudhop T, von Bergman K. Effect of garlic oil preparation on serum lipoproteins and cholesterol metabolism: a randomized, controlled trial. *JAMA*. 1998;279:1900-1902.
- Lawson D. *Human Medicinal Agents From Plants*. Springville, Utah: American Chemical Society; 1993.
- Jain A, Vargas R, Gotskowsky S, McMahon F. Can garlic reduce the levels of serum lipids? a controlled clinical study. *Am J Med*. 1993;94:632-635.
- Adler AJ, Holub BJ. Effect of garlic and fish oil supplementation on serum lipid and lipoprotein concentrations in hypercholesterolemic men. *Am J Clin Nutr*. 1997;65:445-450.
- Steiner M, Khan AH, Holbert D, Lin R. A double-blind crossover study in moderately hypercholesterolemic men that compared the effect of aged garlic extract and placebo administration on blood lipids. *Am J Clin Nutr*. 1996;64:866-870.
- Silgay C, Neil A. A meta-analysis of the effect of garlic on blood pressure. *J Hypertens*. 1994;12:463-468.
- Kleijnen J, Knipschild P, Ter Riet G. Garlic, onions and cardiovascular risk factors: a review of the evidence from human experiments with emphasis on commercially available preparations. *Br J Clin Pharmacol*. 1989;28:535-544.
- Yamahara J, Huang Q, Li Y, Xu L, Fujimura H. Gastrointestinal motility enhancing effect of ginger and its active constituents. *Chem Pharm Bull*. 1990;38:430-431.
- Mascolo N, Jain R, Jain S, Capasso F. Ethnopharmacologic investigations of ginger (*Zingiber officinale*). *J Ethnopharmacol*. 1989;27:129-140.
- Fischer-Rasmussen W, Kjaer S, Dahl C, Asping U. Ginger treatment of hyperemesis gravidarum. *Eur J Obstet Gynecol Reprod Biol*. 1991;38:19-24.
- Phillips S, Ruggier R, Hutchinson S. *Zingiber officinale* (ginger): an antiemetic for day surgery. *Anaesthesia*. 1993;48:715-717.
- Bone M, Wilkinson D, Young J, Charlton S. The effect of ginger root on postoperative nausea and vomiting after major gynecologic surgery. *Anaesthesia*. 1990;45:669-671.
- Arfeen Z, Owen H, Plummer J, Isles A, Sorby-Adams R, Doecke C. A double-blind random controlled trial of ginger for the prevention of postoperative nausea and vomiting. *Anaesth Intensive Care*. 1995;23:449-452.
- Mowbrey D, Claydon D. Motion sickness, ginger, and psychophysics. *Lancet*. 1982;1:656-657.
- Stewart J, Wood M, Wood C, Mims M. Effects of ginger on motion sickness susceptibility and gastric function. *Pharmacology*. 1991;42:111-120.
- Hopfenmuller W. Evidence for a therapeutic effect of Ginkgo biloba special extract: meta-analysis of 11 clinical trials in patients with ce-

- rebovascular insufficiency in old age. *Arzneim Forsch.* 1994;44:1005-1013.
55. Kleijnen J, Knipschild P. Ginkgo biloba for cerebral insufficiency. *Br J Clin Pharmacol.* 1992;34:352-358.
  56. Le Bars P, Katz M, Berman N, Turan M, Freedman A, Schatzberg A. A placebo-controlled, double-blind, randomized trial of an extract of *Ginkgo biloba* for dementia. *JAMA.* 1997;278:1327-1332.
  57. Hindemarch I, Subhan Z. The pharmacological effects of *Ginkgo biloba* extract in normal healthy volunteers. *Int J Clin Pharmacol Res.* 1984;4:89-93.
  58. Ernst E. Ginkgo biloba extract in peripheral arterial diseases: a systematic research based on controlled studies in the literature. *Fortsch Med.* 1996;114:85-87.
  59. Roncin J, Schwartz F, D'Arbigny P. EGb 761 in control of acute mountain sickness and vascular reactivity to cold exposure. *Aviat Space Environ Med.* 1996;67:445-452.
  60. Behl C, Davis J, Leslie R, Schubert D. Hydrogen peroxide mediates amyloid B protein toxicity. *Cell.* 1994;77:817-827.
  61. Maitra I, Marcocci L, Droy-Lefais M, Packer L. Peroxyl radical scavenging activity of Ginkgo extract EGb 761. *Biochem Pharmacol.* 1995;49:1649-1655.
  62. Knapp M, Knopman D, Solomon P. A 30-week randomized controlled trial of high dose tacrine in patients with Alzheimer's disease. *JAMA.* 1994;271:985-991.
  63. Rogers SL, Doody RS, Mohs RC, Friedhoff LT. Donepezil improves cognition and global function in Alzheimers disease: a 15-week, double-blind, placebo-controlled study. *Arch Intern Med.* 1998;158:1021-1031.
  64. Woerdenbag HJ, Van Beck TA. *Ginkgo Biloba. Adverse Effects of Herbal Drugs. Vol 3.* Berlin, Germany: Springer-Verlag; 1997.
  65. Kleijnen J, Knipschild P. *Ginkgo biloba.* *Lancet.* 1992;340:1136-1139.
  66. Lawrence Review of Natural Products. *Ginseng.* St Louis, Mo: Facts and Comparisons; 1990.
  67. Marasco C, Vargas R, Salas V, Begona I. Double-blind study of a multivitamin complexes supplemented with ginseng extract. *Drugs Exp Clin Res.* 1996;22:323-329.
  68. Bahrke M, Morgan W. Evaluation of the ergogenic properties of ginseng. *Sports Med.* 1994;18:229-248.
  69. D'Angelo R, Grimaldi M, Caravaggi M, et al. A double-blind, placebo-controlled clinical study on the effect of a standardized ginseng extract on psychomotor performance in healthy volunteers. *J Ethnopharmacol.* 1986;16:15-22.
  70. Salvati G, Genovesi G, Marcellini L, et al. Effects of *Panax ginseng* C. A. Meyer saponins on male fertility. *Panminerva Med.* 1996;38:249-254.
  71. Taik-Koo Y, Soo-Yong C. Preventive effect of ginseng intake against various human cancers: a case-control study on 1987 pairs. *Cancer Epidemiol Biomarkers Prev.* 1995;4:401-408.
  72. Chin R. Ginseng and common pregnancy disorders. *Asia Oceania J Obstet Gynecol.* 1991;17:379-380.
  73. Castleman M. Ginseng. *Herb Q.* 1990;48:17-24.
  74. Siegel R. Ginseng abuse syndrome. *JAMA.* 1979;241:1614-1615.
  75. Palmer B, Montgomery A, Monteiro J. Ginseng and mastalgia [letter]. *BMJ.* 1978;1:1284.
  76. Rabbani G, Butler T, Knight J, Sanyai S, Alam K. Randomized controlled trial of berberine sulfate therapy for diarrhea due to enterotoxigenic *Escherichia coli* and *Vibrio cholerae*. *J Infect Dis.* 1987;155:979-984.
  77. Choudhry V, Sabir M, Bhide V. Berberine in giardiasis. *Indian J Pediat.* 1972;9:143-144.
  78. Bergner P. Goldenseal and the common cold. *Med Herbalism.* 1997;8:1,4-6.
  79. Foster S. Goldenseal: *Hydrastis canadensis.* American Botanical Council Series. 1991:309.
  80. Sun D, Courtney H, Beachey E. Berberine sulfate blocks adherence of *Streptococcus pyogenes* to epithelial cells, fibronectin, and hexadecane. *Antimicrob Agents Chemother.* 1988;32:1370-1374.
  81. Sack R, Froehlich J. Berberine inhibits intestinal secretory response of *Vibrio cholera* toxins and *Escherichia coli* enterotoxins. *Infect Immun.* 1982;35:471-475.
  82. Lawrence Review of Natural Products. *Goldenseal.* St Louis, Mo: Facts and Comparisons; 1994.
  83. Newall C, Anderson L, Phillipson J. *Herbal Medicines: A Guide for Health-Care Professionals.* London, England: Pharmaceutical Press; 1996.
  84. Ferenci P, Dragosics B, Ditttrich H, et al. Randomized controlled trial of silymarin treatment in patients with cirrhosis of the liver. *J Hepatol.* 1989;9:105-113.
  85. Pares A, Planas R, Torres M, et al. Effects of Silymarin in alcoholic cirrhosis of the liver: results of a controlled, double-blind, randomized and multicenter trial. *J Hepatol.* 1998;28:615-621.
  86. Velussi M, Cernigoi A, Viezzoli L, Dapas F, Carrau C, Zilli M. Silymarin reduces hyperinsulinemia, malondialdehyde levels and daily insulin need in cirrhotic diabetic patients. *Curr Ther Res.* 1993;53:533-545.
  87. Buzzelli G, Moscarella S, Giusti A, Duchini A, Marena C, Lampertico M. A pilot study on the liver protective effect of silybin-phosphatidylchlorine complex (dB 1016) in chronic active hepatitis. *Int J Clin Pharmacol Ther Toxicol.* 1993;31:450-460.
  88. Lawrence Review of Natural Products. *Milk Thistle.* St Louis, Mo: Facts and Comparisons; 1994.
  89. Muriel P, Garciaipina T, Perez-Alvarez V, Mourelle M. Silymarin protects against paracetamol-induced lipid peroxidation and liver damage. *J Appl Toxicol.* 1992;12:439-442.
  90. Davila J, Lenher A, Acosta D. Protective effect of flavonoids on drug-induced hepatotoxicity in vitro. *Toxicology.* 1989;57:267-286.
  91. Letteron P, Labbe G, Cegott C, et al. Mechanism for the protective effects of silymarin against carbon tetrachloride-induced lipid peroxidation and hepatotoxicity in mice. *Biochem Pharmacol.* 1990;39:2027-2034.
  92. Pietrangelo A, Borella F, Casalgrandi G. Antioxidant activity of silybin in vivo during long term iron overload in rats. *Gastroenterology.* 1995;109:1941-1949.
  93. Gaedeke J, Fels L, Bokemyere C. Cisplatin nephrotoxicity and protection by silibinin. *Nephrol Dial Transplant.* 1996;11:55-62.
  94. NIH. NIH to explore St. John's wort. *Science.* 1997;278:391.
  95. Linde K, Gilbert R, Murlow C, Pauls A, Weidenhammer W, Melchart D. St. John's wort for depression: an overview and meta-analysis of randomized clinical trials. *BMJ.* 1996;313:253-257.
  96. St. Johns wort (*Hypericum perforatum*): quality control, analytical and therapeutic monograph. *Am Herbal Pharmacopoeia.* 1997:1-38.
  97. Muller W. Effects of *Hypericum* extract on the suppression of serotonin receptors. *J Geriatr Psychiatry Neurol.* 1994;7:S63-64.
  98. Buck A. Phytotherapy for the prostate. *Br J Urol.* 1996;78:325-336.
  99. Lowe F, Ku J. Phytotherapy in treatment of BPH: a critical review. *Urology.* 1996;48:12-20.
  100. Smith R, Mermon A, Smart C, et al. The value of permixon in benign prostatic hypertrophy. *Br J Urol.* 1986;58:36-40.
  101. Descotes J, Rambeaud J, Deschaseaux P, Faure G. Placebo-controlled evaluation of the efficacy and tolerability of permixon in benign prostatic hyperplasia after exclusion of placebo responders. *Clin Drug Invest.* 1995;9:291-297.
  102. Carraro J, Raynaud J, Koch G. Comparison of phytotherapy (Permixon) with finasteride in the treatment of BPH: a randomized international study of 1098 patients. *Prostate.* 1996;29:23:1-240.
  103. Di Silverio F, D'Eramo G, Lubrano C, et al. Evidence that *Serenoa repens* extract displays an antiestrogenic activity in prostatic tissue of benign prostatic hypertrophy patients. *Eur Urol.* 1992;21:309-314.
  104. Braekman J. The extract of *Serenoa repens* in the treatment of BPH: a multicenter open study. *Curr Ther Res.* 1994;55:776-785.
  105. Sultan C, Terraza A, Devillier C. Inhibition of androgen metabolism and binding by a liposterolic extract of "*Serenoa repens* B" in human foreskin fibroblasts. *J Steroid Biochem.* 1984;20:515-519.
  106. Grasso M, Montesano A, Buonaguidi A, et al. Comparative effects of alfuzosin versus *Serenoa repens* in the treatment of symptomatic benign prostatic hyperplasia. *Arch Esp Urol.* 1995;48:97-103.
  107. Lepor H, Williford W, Barry M, et al. The efficacy of terazosin, finasteride, or both in benign prostatic hyperplasia. *N Engl J Med.* 1996;335:533-539.
  108. Leatherwood P, Chauffard F, Heck E, Munoz-Box E. Aqueous extract of valerian root (*Valeriana officinalis* L.) improves sleep quality in man. *Pharmacol Biochem Behav.* 1982;17:6541.
  109. Lindahl O, Lindwell L. Double-blind study of a valerian preparation. *Pharmacol Biochem Behav.* 1989;32:1065-1066.
  110. Leuschner J, Muller J, Rudmann M. Characterization of the central nervous depressant activity of a commercially available valerian root extract. *Arzneim Forsch.* 1993;43:638-641.
  111. Mennini T, Bernasconi P, Bombardelli E, Morazzoni P. In vitro study of the interaction of extracts and pure compounds from *Valeriana officinalis* roots with GABA, benzodiazepine and barbiturate receptors in rat brain. *Fitoterapia.* 1993;54:291-300.
  112. Hobbs C. Valerian: a literature review. *Herbal Gram.* 1989;21:19-34.