Herbals and other Dietary Supplements in the United States, Part II: Popular Herbal Remedies

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Learning Objectives
After completing this continuing education program, the pharmacist will be able to:

1. Classify the most popular herbs in use, the plant parts and extracts derived therefrom.
2. Identify the most common uses for these herbs and the objective evidence supporting or refuting these uses.
3. Discuss the most common adverse effects of popular herbs.
4. Recall the most important drug interactions and clinical relevance to patients taking herbs.

Abstract: Safety and efficacy issues surrounding the use of the most popular herbs are discussed. The various herbs classified under the general heading "ginseng" are compared and contrasted. Echinacea is commonly used for treating colds and flu. St. John's Wort is among the best studied herbs in terms of efficacy in treating depression and drug interactions. Saw palmetto is used to treat benign prostatic hypertrophy with a minimum of side effects and drug interactions. Garlic has a wide range of uses, including hyperlipidemia, hypertension, and infections. Kava kava shows promise as an alternative for mild anxiety disorders. Valerian has been used with some success to treat insomnia. Ginkgo has gained acceptance for treating dementia, memory loss, and intermittent claudication. Goldenseal is a popular but probably ineffective antiseptic and agent for masking drug screens. Milk thistle may have a role in treating liver disease of various origins. Aloe is used as a laxative and to treat wounds. Black cohosh is a popular herb for treating the symptoms of menopause.

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NARRATIVE

The most popular herbs are discussed. Included are ginseng, echinacea, St. John's Wort, saw palmetto, garlic, kava kava, valerian, ginkgo, goldenseal, milk thistle, aloe, and black cohosh. Emphasis is placed on objective evidence for safety and efficacy, along with evidence for drug interactions.

INTRODUCTION

Patients continue to embrace herbs. This adds a new dimension to patient history-taking and effective patient care. However, the number of herbs available and volume of evaluable literature are expanding at a dramatic rate. Which herbs are patients most likely to use? What is known about the most popular herbs? Are they safe for use? Do they actually work? Is the whole plant used, or an extract of a particular plant part? Do these herbs interact with medications? Are there side effects? Part I of this series indicated which medical conditions and patient characteristics predispose patients to use herbs.[1] It also outlined some of the most popular herbs. In Part II, some of these most popular herbs will be reviewed, with an eye to pertinent information that could impact patient care.

POPULAR HERBS

Ginseng (*Panax ginseng* [*P. ginseng*], *Panax quinquefolius* [*P. quinquefolius*], *Eleuthrococcus senticosus* [*E. senticosus*])

Ginseng consistently appears as one of the top three used herbs in surveys.[1] Unfortunately, it is also among the most misunderstood of the popular herbs. No other herb is associated with as much history or mystique. The root or rhizome has been used medicinally in Asia for over 5 centuries. It was used as a general health tonic and aphrodisiac. Its traditional use may have stemmed, in part, from the resemblance the rhizome bears to a small man. According to the old treatment concept "Doctrine of Signatures," a plant that resembles an organ could be used to treat maladies. For this reason, ginseng gained a reputation as a "cure-all" or panacea.[2] Volumes have been written on its uses, effects, and pharmacology. Russian scientists coined the term "adaptogen" to describe ginseng's properties. An adaptogen is a compound that increases resistance to stress in both the healthy and the sick, improves vitality, and restores homeostasis to the body without side effects. In the United States, ginseng is also perceived to increase mental alertness, to combat fatigue, and to help prevent disease.[3] It is also popular among athletes for increasing physical performance.

Most people understand the term "ginseng" to mean Korean ginseng (*P. ginseng*). Korean ginseng root takes 5 years or more to grow in cultivation. As a result, it is expensive, with prices ranging from $20 to several thousand dollars an ounce. The closely related American ginseng (*P. quinquefolius*) is so highly sought after in the United States that it has become an endangered species as a result of the overharvesting of wild sources.[2]

In an effort to find less expensive substitutes, the term "ginseng" has acquired generic connotations, as various plant species are purported to have adapatogen properties. Research by the Russian scientist I.I. Brechkman on the species *E. senticosus* (eleuthro or ciwujia) led him to conclude that it was similar in properties to *P. ginseng*. The misleading term "Siberian ginseng" was coined despite that eleuthro is only distantly related to, and chemically distinct from, the *Panax* species. Another unrelated species, called canagrie, was known as wild red desert

ginseng. Although promoted for a wide range of ailments, including lack of vitality, its uses were not supported in the early herbal literature. Indeed, the Native Americans most commonly used it as a tanning agent because of its 18% to 25% tannin content. Although the Herb Trade Association adopted a policy statement in 1979 stating that products containing canagrie should not be labeled "ginseng," it is still listed as such in several pre-1980 herbals.[2]

The use of the generic term "ginseng" makes it difficult for the consumer to know whether s/he has received the true ginseng or not. This is further compounded because ginseng has also contained contaminants, including caffeine, the highly toxic and anticholinergic mandrake, the nephrotoxic germanium, and the hypotensive snakeroot. Several surveys of ginseng products have failed to find active ingredients. One survey failed to find any ginseng in 25% of the assayed products, with another 60% containing so little ginseng as to be deemed "worthless." A survey of products in 1995 found a wide degree of variability of the ginsenoside content, the constituent used to identify and standardize *P. ginseng*.[2]

Eleuthro (Siberian ginseng) has been particularly popular for use among athletes. Clinical trials have yielded varying results. Healthy subjects who took an eleuthro extract called Taiga Wurzel for 30 days demonstrated increased oxygen use during exercise in healthy subjects, as well as improvements in lipid profiles and cellular defense.[5] Other eleuthro preparations failed to increase oxygen use or other parameters of exercise efficiency when taken for 1-6 weeks.[3,6] Small clinical trials have demonstrated significant improvements ($P < 0.02$) in selective memory tests when compared with placebo. The eleuthro extract Elagan demonstrated a 75% decrease in the frequency, severity, and duration of Herpes infections versus 34% for placebo in 93 subjects.[3] Eleuthro is usually well-tolerated. Although not much is known about its interactions with medications, animal data suggest that eleuthro extracts may potentiate the effects of barbiturates by inhibiting their metabolism.[7]

Preliminary evidence suggests that American ginseng (*P. quinquefolius*) may lower blood sugar concentrations in patients with type 2 diabetes mellitus. In a placebo-controlled trial, 3 g of American ginseng had no effect on postprandial glycemia in nondiabetic patients when taken simultaneously with a glucose challenge, but significantly ($P < 0.05$) decreased postprandial glycemia when administered 40 minutes prior to the test. In those with type 2 diabetes, ginseng significantly ($P < 0.05$) decreased postprandial hyperglycemia whether taken with or 40 minutes prior to the challenge. The area under the glycemic curve was significantly decreased in both nondiabetic and diabetic patients.[8] The effect is time- but not dose-dependent in healthy individuals.[9]

Although much touted for its general uses, little research supports the adaptogenic claims made for *P. ginseng*. The research is further confounded because in many early trials, the species of ginseng or product was not clearly characterized or identified. The variability of ginseng products on the market further confounds these findings. One 12-week, double-blind, placebo-controlled trial of ginseng's immunostimulating effects found a significant decrease in the frequency of colds and flu in the treatment group ($P < 0.001$), and increased antibody titers in response to the influenza vaccine ($P < 0.0001$). Several double-blind, placebo-controlled, clinical trials have demonstrated improved mental performance with *Panax ginseng*. In 3 trials, healthy young subjects taking *P. ginseng* demonstrated significantly improved capacity for

abstract thinking, ability to complete a detail-oriented task, and ability to perform mental arithmetic. Trials of ginseng on physical performance have had mixed results.[3]

Ginseng abuse syndrome, which included addiction, elevated blood pressure, nervousness, insomnia, and increased libido, was reported in the late 1970s. It has largely been discredited owing to flaws in methods and lack of uniformity in defining a "ginseng" product.[11] The most common side effects are insomnia, diarrhea, and skin eruptions.[2] Data regarding drug interactions are sparse. Because of potential hypoglycemic effects, patients taking insulin, sulfonylureas, or other medications for diabetes should be monitored for additive effects when taking *P. ginseng* or *P. quinquefolius*. *P. ginseng* has been reported to interact with phenelzine to produce insomnia, tremors, headache, and hypomania.[12,13] It is not known whether the ginseng preparations contained contaminants, such as caffeine. Ginseng has decreased the effectiveness of warfarin,[14] but the results were not supported by follow-up research data.[15]

Echinacea *(Echinacea angustifolia [E. angustifolia], Echinacea purpurea [E. purpurea], Echinacea pallida [E. pallida])*

Echinacea, or purple coneflower, is a North American native of the plains, and was widely used by Native Americans. Before antibiotics, echinacea was widely prescribed as a treatment for colds and flu. It was officially listed in the National Formulary from 1916 to 1950. It fell out of favor with the invention of sulfa drugs in the 1930s, despite that antibiotics have no activity against viruses. Although *E. angustifolia* was the primary species used, 9 different species of Echinacea grow in the United States. Only 2 other species, the widely cultivated *E. purpurea* and *E. pallida*, are of medicinal interest.[16] The others present problems when attempting to develop signature standardized extracts. For this reason, the exact species of Echinacea should be identified on product bottles.

Echinacea is most commonly used to prevent and treat colds and other upper respiratory tract illnesses. It is also used as an immunostimulant to treat other infections, including urinary tract infections, vaginal candidiasis, and cancer. Topical preparations are used to treat burns and wounds. It has been used safely in trials lasting up to 12 weeks. Although it has not proved useful in clinical trials for preventing colds, echinacea does appear to decrease the severity and duration of symptoms attributable to the common cold and flu, but only if taken at the first sign of symptoms and continued for 7 to 10 days. The specific preparation used is important. *E. purpurea* extracts of the above-ground plant parts, roots, a 95%/5% combination, or root extracts of *E. pallida* are the ones shown to have clinical benefit. *E. purpurea* herb juice also appears to prevent recurrence of vaginal yeast infections when used orally in combination with topical antifungals.[17,18]

Side effects with echinacea are relatively rare. It should be used with caution in patients who are allergic to members of the Asteraceae/Compositae family. This includes daisies, chrysanthemums, ragweed, and marigolds. Cross-sensitivity to other members of this family does occur.[19] Although it is currently theoretical, Echinacea may interfere with the activity of immunosuppressants. Echinacea is not recommended for patients with autoimmune disorders, such as lupus, rheumatoid arthritis, and multiple sclerosis, or for patients with atopy, as it might, theoretically, worsen their condition. This is also true of patients with other immune disorders, such as human immunodeficiency virus (HIV). In addition, there is some suggestion that Echinacea may inhibit the CYP 3A4 enzyme.[20] This could lead to elevated levels of some

antiretroviral medications, such as non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors.

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

St. John's Wort has been known for its medicinal properties since the time of Hippocrates. It got its name because it reaches its peak bloom season around the time of John the Baptist's celebrated birthday, June 24. This is also the time at which the above-ground plant parts are harvested for medicinal use.[2] St. John's Wort is most commonly used to treat depression, but has also been used to treat obsessive-compulsive disorder, HIV, neuropathy, and secondary symptoms of depression, such as insomnia, fatigue, and loss of appetite.

The active principle of St. John's Wort is not currently known, and activity may be because of a number of constituents. The most studied constituent is hypericin, and it is also the most photosensitizing component of St. John's Wort. Hypericin inhibits both catechol-O-methyl transferase (COMT) and monoamine oxidase (MAO) in vitro, but does not appear to reach concentrations to display these activities clinically. Hypericin also has activity at sigma receptors and antagonistic activity at adenosine, benzodiazepine, γ-aminobutyricacid-A (GABA-A), GABA-B, and inositol triphosphate receptors.[21] Most clinical studies using a hypericin-rich extract used the specific extract called LI 160, standardized to a 0.3% hypericin content.[22-26] Many commercially available St. John's Wort extracts are similarly standardized. Some trials have used the 0.2% hypericin extract ZE-117.[27] Some evidence suggests that hyperforin may also contribute to St. John's Wort's efficacy. Several clinical trials have used hyperforin-rich extracts, such as WS 5572. Hyperforin has non-specific, reuptake inhibition at serotonin, norepinephrine, and dopamine receptors, and downregulates cortical beta-receptors.[28] Other constituents may contribute to the activity of St. John's Wort. [21]

Clinical research suggests that St. John's Wort is most appropriate for the treatment of mild-to-moderate depression, as measured on the Hamilton Depression Index (HAM-D) as a score of 25 or less. Patients with this type of depression have debilitating illness, but not dangerous symptoms, such as active suicidal ideation. St. John's Wort has been significantly more effective than placebo in numerous clinical trials. In one double-blind, crossover trial, 72 patients with an initial average HAM-D score of 21.8 and a DSM-III-R diagnosis of depression experienced a drop in HAM-D scores to 9.2 after 4 weeks of therapy with 300 mg po tid of LI 160, significantly lower than placebo ($P < 0.001$). The response rate was high – over 80% in the treatment group versus 26% in the placebo group.[27] Several meta-analyses, including one from the Cochrane Library, have also suggested superiority of St. John's Wort over placebo for short-term treatment of mild-to-moderate depression.[22,23] One recent clinical trial suggests conflicting results with St. John's Wort extract LI 160 900-1200 mg/day. Of 200 patients with major depression and a HAM-D score of at least 20, significantly more attained clinical remission on LI 160 than placebo ($P = 0.02$). Only 14.9% of patients taking the extract achieved this.[24]

St. John's Wort is also comparable to the selective serotonin reuptake inhibitors (SSRIs) in efficacy. In 240 moderately depressed subjects with HAM-D scores of 16-24, 6 weeks of treatment with 500 mg of ZE 117 was comparable to fluoxetine 20 mg/day. HAM-D scores decreased to 11.54 on ZE 117 and 12.20 on fluoxetine ($P < 0.09$). St. John's Wort was significantly better tolerated than fluoxetine (8% vs. 23%).[27] The extract LoHyp-57 at 800

mg/day was comparable with 20 mg of fluoxetine in 72 mildly depressed and 77 moderately depressed patients (as defined by ICD-9 codes). HAM-D scores dropped from 14.21 to 6.21 points on LoHyp-57, and from 15.21 to 7.46 points on fluoxetine in the mildly depressed patients. In patients with moderate depressive episodes, the score showed a mean fall from 18.73 to 9.43 points on LoHyp-57 and from 19.10 to 8.75 points on fluoxetine.[29] The St. John's Wort extract LI 160 was comparable to 75 mg/day of sertraline in a 6-week trial of 30 depressed patients. HAM-D scores decreased significantly in both groups ($P < 0.01$), with a 47% response rate to LI 160 and a 40% response rate to sertraline (judge as a >50% decrease in HAM-D score).[26] Numerous clinical trials have compared St. John's Wort with tricyclic antidepressants, but at subclinical doses of the latter.[23] The highest dose of tricyclic used was 150 mg/day of imipramine vs. 1800 mg/day of LI 160. Imipramine was superior to LI 160 after 6 weeks of therapy. LI 160 dropped HAM-D scores from 25.3 to 14.4, similar to impramine (26.1 to 13.4). However, only 35.2% of patients responded to LI 160 vs. 42.1% of patients on imipramine ($P < 0.01$).[30]

St. John's Wort is usually well-tolerated. In clinical trials, the most common side effects were gastrointestinal (GI) disturbances. When used in daily doses of 1800 mg or more, it may induce phototoxic reactions.[11] It has also induced hypomania in a bipolar patients.[31,32]

Because St. John's Wort interacts with a number of medications, it is not necessarily advised in patients taking prescription medications. Because St. John's Wort may inhibit serotonin reuptake, it should not be given with other serotonergic drugs. Serotonin syndrome has occurred in patients taking St. John's Wort concomitantly with nefazodone, paroxetine, and sertraline.[33-35] In addition, St. John's Wort induces CYP 3A4 and increases expression of intestinal P-glycoprotein.[36] St John's Wort has decreased cyclosporine concentrations, resulting in organ rejection in transplant patients.[37-39] It also significantly decreased concentrations of the protease inhibitor indinavir, and can subsequently lead to therapeutic failure of HIV regimens.[40] St. John's Wort can also lead to decreased PT/INR ratios in patients taking warfarin, probably attributable to induction of CYP 1A2.[41] It also decreases digoxin concentrations, but does not decrease carbamazepine plasma concentrations.[42]

Saw palmetto (*Serenoa repens*)

Saw palmetto was listed in the National Formulary until the 1950s as a treatment for benign prostatic hypertrophy (BPH).[2] Although the active principles reside in the lipophilic fraction of saw palmetto, the exact identity of the constituent is not known. Most studies have used an 80%-90% fatty acid extract called Permixon. Saw palmetto is appropriate only for the treatment of mild-to-moderate BPH, not severe cases in which severe urinary retention is involved. The fatty acid beta-sitosterol has been the focus of some research because of its anti-inflammatory properties, but its proposed mechanism of action is not fully elucidated.[43] Saw palmetto extracts, but not beta-sitosterol, inhibited in vitro binding of tamsulosin and prazosin to human prostatic alpha-adrenergic receptors, activity in a noncompetitive fashion.[44] These same extracts also inhibited phenylephrine-induced inositol formation. The relationship between in vitro concentrations and therapeutic doses of saw palmetto was slightly less than that of alpha blockers. Saw palmetto extracts do not appear to have alpha-adrenergic blocking activity when given to healthy young men.[45] Although in vitro data suggest that saw palmetto might noncompetitively inhibit 5-alpha-reductase types 1 and 2, it did not affect 5-alpha-reductase

levels in prostatic tissue. Saw palmetto does not appear to have effects on prostate-specific antigen (PSA) concentrations. It also does not appear to appreciably decrease prostate size, although it appears to shrink inner epithelial tissue. [43,46]

Trials comparing saw palmetto extract with placebo in the treatment of BPH have yielded mixed results, but have, in general, positive effects. A meta-analysis of trials suggested that when compared with placebo, saw palmetto extracts resulted in a 1.93 mL/second (24%) improvement in peak urinary flow, 2.22 mL/second (28%) improvement in mean urine flow, 22.05 mL (43%) in residual urine flow, 25% reduction in nocturia, and 2.14 cc decrease in prostate size.[46] Permixon at 160 mg/day was comparable to finasteride 5mg/day in symptom relief. [46,47] The trials contained some flaws. Finasteride is known to be more effective in men with prostate sizes greater than 40-50 mL, and may take 6 months or longer to effect clinical results. Saw palmetto itself takes approximately 1-2 months to show effects. Unlike finasteride, saw palmetto has no effect on serum testosterone concentrations.[48] Two studies comparing saw palmetto extract with alpha-blockers (prazosin and alfuzosin) suggest that saw palmetto is inferior for treatment of symptoms.[49,50]

Saw palmetto has a low incidence of side effects. The most common are mild GI disturbances and headache. There are no know drug interactions, but no formal studies have been undertaken. Although saw palmetto products may carry claims that it "promotes a healthy prostate," there is currently no clinical data to support its use for prophylaxis of BPH.

Garlic (*Allium sativum*)

Although garlic is probably best known for its use in treating hyperlipidemia, it has been used for multiple medical conditions. The most prominent of these are hypertension and to treat a wide range of infections. Two components of garlic contribute to much of its activity. Allicin and ajoene are not present in an intact garlic clove. When the clove is smashed, alliin comes in contact with allinase to make allicin, which further condenses to ajoene. Allinase is heat-labile, allicin is acid-labile; for this reason, garlic preparations must be prepared in a manner to preserve the active components.[2]

Results of trials using garlic to treat hyperlipidemia have been mixed. Some of these differences can be accounted for in the earlier trials by lack of consistency in the preparation used, failure to detect active or standardized constituents, or trial design flaws. Meta-analyses show that garlic may lower total serum cholesterol by 4.3%-12%.[51-53] However, even trials using the same aged garlic powder preparation (Kwai) have yielded conflicting results. In one trial, Kwai at 900 mg/day was found to be comparable to bezafibrate 600 mg.[54] In another trial, garlic was found to be inferior to clofibrate.[55]

Garlic may lower blood pressure, but most of the trials that investigated this effect contained method flaws. A meta-analysis examining the hypotensive effects of garlic found only 3 of the 8 trials met the criteria for inclusion in analysis. Two trials that used 600 mg of Kwai daily for 12 weeks in hypertensive subjects demonstrated an average 11.1 mm Hg decrease in systolic and 6.5 mm Hg decrease in diastolic blood pressure over placebo. However, patients in one of these trials had unequal baseline blood pressures, bringing the results into question.[56]

Garlic also appears to have a wide range of antimicrobial activity, encompassing antibacterial, antifungal, antiviral, and antiprotozoal activity. Most of the current information is based on in vitro and animal data. The proposed antibacterial mechanism is the binding of allicin and ajoene to the cysteine groups of enzymes essential for bacterial proliferation.[57,58] Garlic has extensive in vitro activity against both gram-positive and gram-negative bacteria. In general, aerobic bacteria are more susceptible than anaerobic. One milligram of allicin is approximately equivalent to 15 U of penicillin (10 mcg), or 1% of penicillin's activity.[59] Garlic juice containing 220 mg extract/mL was equivalent to 30 mcg chloramphenicol, 5 mcg kanamycin, 300 mcg nitrofuratoin, 10 mcg ampicillin, and 10 mcg streptomycin by the disc diffusion test using a total of 12 gram-positive and gram-negative bacteria. Chloramphenicol-resistant strains of *E. coli* and *Proteus sp.* were inhibited by the garlic juice.[59] Although initial trial results suggested a role in treating *Helicobacter pylori*, subsequent trials have failed to demonstrate efficacy in humans.[60] The antifungal activity of garlic includes *Histoplasma capsulatum*, Torulopsis, Trichosporon, *Candida albicans*, Aspergillus sp. and dermatophytes.[61] Although data on antiviral effects is limited, garlic has activity against herpes simplex I and II, vaccinia, vesicular stomatitis, and human rhinovirus. Ajoene is the most active component.[62] The garlic component diallyl trisulfide has activity against *Entamoeba histolytica*, *Giardia lamblia*, and *Trichomonas vaginalis*.[63]

Side effects with garlic are usually limited to GI disturbances and odor, depending on the preparation used. Because garlic also has antiplatelet and antithrombotic effects, it should not be taken with antiplatelet agents or anticoagulants. Garlic may also decrease the efficacy of medications metabolized by cytochrome P450 enzyme 3A4, including cyclosporine, oral contraceptives, and protease inhibitors.[64]

Kava Kava (*Piper methysticum*)

Kava kava has a long tradition of use as a ceremonial drink in the Pacific Islands to induce a relaxed state. Outside of the South Pacific, it is most commonly used to treat anxiety disorders and related symptoms, such as insomnia, restlessness, and stress. It does not appear to have activity through either the benzodiazepine or GABA receptors. Most clinical trials have used an extract standardized to 70% kavalactones called WS 1490 (Laitin). Several clinical trials have shown WS 1490 to be superior to placebo. As much as 1-8 weeks of treatment may be needed in order to note improvement.[65-67] WS 1490 was also comparable with low-dose benzodiazepines. In patients with a HAMA-A score of >18, a daily dose of either WS 1490 300 mg, 15 mg of oxazepam, or 9 mg of bromazepam decreased HAMA-A scores from a range of 38.5-40 to a range of 26-28.5 (*P* values not given). No differences were noted among the groups. Decreases in symptoms were evident after the first week of therapy.[68] Unlike benzodiazepines, kava does not appear to impair cognitive or motor function. This may be dependent on the dosage form taken, as drug utilization reviews (DUIs) have been issued to subjects who have taken large quantities of kava tea.[69,70]

Hepatitis has been associated with kava use. One case resulted in hospitalization and liver transplant. The symptoms occurred after the man took a kava dose equivalent to approximately 210-280 mg kavalactones for one month. Although the association of hepatitis with kava was judged probable, no analysis of the product was performed to verify the presence of kava or rule out hepatotoxic herbs. In other cases, it is not clear whether the hepatitis was because of kava or

concomitantly ingested substances.[71] Long-term use of kava root in native Polynesians has been associated with a dermopathy characterized by yellow-discoloration and dry, flaky skin. It is nonresponsive to niacinamide therapy, and reverses upon discontinuation of kava.[11] A case of coma occurring from concomitant ingestion of kava and alprazolam has occurred. For this reason, kava should not be combined with CNS depressants, such as benzodiazepines, alcohol, or barbiturates.[72]

Valerian (*Valeriana officinalis*)

Valerian is most commonly used as a sedative-hypnotic in the treatment of sleep disorders, and was included as a sleep aid in the National Formulary until 1950. The active constituents of valerian aren't currently known, but have been attributed to the valepotriates and the volatile oils, including the sesquiterpenes and monoterpenes. Although valepotriates induce sedation in rats, they are not likely to be present in high enough amounts to be responsible for valerian's effects. Indeed, valerian derives its distinctive smell, which has been compared with "stinky socks," from breakdown products of the valepotriates, isovaleric acid. It is also not clear how these active constituents act centrally to induce sedation. Research data have suggested that valerian extracts may bind weakly to benzodiazepine, GABA, or barbiturate receptors or increase GABA concentrations in the synaptic cleft.[73]

Valerian has been safely used in patients in trials lasting up to 28 days. It may not be as safe when used for longer periods of time. Small clinical trials have consistently demonstrated a significant decrease in sleep latency and a subjective perception of improved sleep in subjects taking valerian when compared with placebo. It also improves mood and decreases early awakening.[11] Even though valerian is commonly recommended for occasional insomnia, it may, in fact, be more effective when taken over a longer time period. Clinical trials have yielded conflicting results regarding the most appropriate use of valerian. The ethanolic valerian extract LI156 showed no statistically significant effects on sleep over placebo at 14 days, but did statistically improve clinical results by 28 days, as measured by the Clinical Global Scale (CGI) and von Zerssen Mood Scale ($P < 0.001$).[74] In another trial in which 128 subjects received either 400 mg of freeze-dried aqueous valerian extract or placebo for three nights, subjects reported significant improvements in sleep with valerian.[75] Valerian extract LI 156 (600 mg) was as effective as oxazepam 10 mg for improving sleep quality when given 30 minutes before bedtime to 74 patients with insomnia for 28 days.[76]

Valerian is generally well-tolerated, although some clinical trials have reported morning sedation. Unlike flunitrazepam (1 mg), a single dose 600 mg of LI 156 did not impair reaction abilities, concentration, and coordination. LI 156 dosing was no different than placebo in its effects when continued for two weeks.[77] Nevertheless, a registered valerian tincture in Germany is required to include labeling that warns about possible reduced ability to drive or operate heavy machinery.[78] Valerian may also occasionally cause headache or mild GI distress. Hepatotoxicity has been reported with use of sleep aids containing a combination of valerian and skullcap. These preparations may have been contaminated by the known hepatotoxin germander.[79] One case of valerian withdrawal syndrome has been reported, but causality could not be determined attributed to complicating factors. No formal interaction with alcohol or benzodiazepines has been demonstrated, but valerian should probably not be given with these or other sedative medications because of the potential for additive effects.[80]

Ginkgo biloba

Although ginkgo has become a prominent dietary supplement for the treatment of dementia, it is also used for intermittent claudication, age-related memory loss, tinnitus, and sexual dysfunction owing to selective serotonin reuptake inhibitor (SSRI) therapy. Neither the mechanism of action nor the active components have been clearly identified. Clinical trials have primarily used one of two ginkgo leaf extracts, Egb 761 or LI 1370. Both extracts are standardized to contain 24% ginkgo-flavone glycosides and 6% terpenoids, of which 2.8% to 3.4% is ginkgolides A, B, and C, and 2.6% to 3.2% isbiolobalide. Ginkgolic acid, which is toxic and can cause severe allergic reactions, should be kept under 5 ppm. For this reason, patients should avoid the use of homemade, crude, or unstandardized ginkgo preparations[2] Numerous theories have been postulated for ginkgo's mechanism of action. Ginkgo extracts increase capillary blood flow. Ginkgo leaf flavinoids have antioxidative and free-scavenging activities. There is also a suggestion that the various components of ginkgo work synergistically.[11]

In clinical trials, ginkgo has been more effective than placebo in treating dementia of both Alzheimer's and non-Alzheimer's origins. One 52-week trial of ginkgo at a daily Egb 761 dose of 120 mg versus placebo in 309 patients demonstrated a delay in progression equivalent to about 6 months in the ginkgo group, whereas the placebo patients showed a progressive decline.[81] In one conflicting trial, treatment with ginkgo failed to improve dementia in 241 patients treated for 24 weeks.[82]

Many patients take ginkgo hoping to prevent dementia or treat mild memory deficits. Several clinical trials suggest that ginkgo may improve memory in patients exhibiting mild to moderate, age-related memory deficits. Clinical trials used doses of 120-240 mg over at least 3 months. In most trials, doses over 120 mg per day were not found to confer further benefit.[83-85] One clinical trial contradicts these results, and failed to find any benefit.[82] Ginkgo at doses ranging from 60 to 600 mg per day may improve certain mental tasks, such as rapid performance of attention-related tasks and short-term memory.[87.88] However, one trial in 19- to 30-year-old women failed to find any benefits.[89]

Ginkgo improves pain-free walking distance in patients with Fontaine stage II peripheral arterial disease. In 74 patients, pain-free walking distance improved 100% with a dose of 120 mg twice daily versus 60% on 60 mg twice daily.[90] It also appears to help reverse the impotence and anorgasmia associated with SSRI therapy. Women (n = 33) had a 91% response rate versus a 71% (n = 30) response rate for men. Improvement was noted in all 4 phases of excitement, at doses of 60-120 mg per day of ginkgo.[91]

Although ginkgo is relatively well-tolerated, it may increase the risk for bleeding. Four case reports of either subdural hematoma or hyphema exist. In one case, ginkgo was taken concomitantly with aspirin. For this reason, ginkgo should not be given with either antiplatelet agents or anticoagulants, such as warfarin.[2] The cyanogenic glycosides in ginkgo seeds are extremely toxic, and ginkgolic acid in ginkgo fruit can cause severe adverse reactions, allergenic, including severe cross-reactivity in patients allergic to poison ivy, poison oak, or poison sumac.[101]

Goldenseal

Goldenseal is a popular antiseptic for treating respiratory and urinary tract infections. It is commonly found combined with echinacea. There is also a popular belief that goldenseal can block a drug screening test. Goldenseal's popularity has led to overharvesting from wild sources, and it is an endangered species as a result. The primary active ingredients are believed to be hydrastine and berberine.[2] Berberine has a wide range of activity against bacteria and fungi, including *Corynebacterium diphtheriae*, *Chlamydia aureus*, *Salmonella typhi*, *Diplococcus pneumoniae (Streptococcus pneumoniae)*, *Pseudomonas aeruginosa*, *Shigella dysenteriae*, *Trichomonas vaginalis*, *Neisseria gonorrhoeae*, *Neisseria meningitidis*, *Treponema pallidum*, *Leishmania donovani*, and fungi. It also stimulates bile secretion. Little evidence exists to support the use of goldenseal to treat systemic infections, including colds and flu. Neither berberine nor hydrastine is absorbed systemically to any great extent, but does concentrate in the bladder. For this reason, antiseptic properties are likely to be limited to topical applications as best. Berberine does significantly decrease the hypersecretion associated with *E. coli*-induced diarrhea, but at doses of goldenseal, too high to be relevant. It also has some minor effects on Vibrio-induced diarrhea, but no additive effects when given with tetracycline.[93] Goldenseal failed to result in false negative tests for marijuana, cocaine, amphetamines, barbiturates, benzodiazepines, opioids, or phencyclidine when assessed via immunoassay (EMIT or TDx) or Microgenics CEDIA DAU assays.[94,95] Goldenseal is considered unsafe for use in pregnancy. It has oxytocic effects, and can displace bilirubin from albumin, increasing the risk for kernicterus in newborns.[93]

Milk Thistle

Milk thistle is most commonly used as a hepatoprotectant. It is also used intravenously in Europe to treat poisonings with the mushroom, *Amantia phalloides*. An extract of the milk thistle fruits or seeds standardized to 70% silymarin, a mixture of 4 isomers (silibinin, isosilybin, silydianin, and silychristin), is used to treat chronic liver disease. Of the 4 isomers, silibinin (or silybin) appears to be the most active. Silymarin undergoes enterohepatic circulation and achieves high concentrations in the hepatocytes. In vitro and animal studies suggest protective effects against toluene, xylene, thioacetamide, praseodymium, polycyclic aromatic hydrocarbons, acetaminophen, carbon tetrachloride, phalloidin, and tetrachloromethane. It appears to work by altering the outer hepatocyte cell membrane to decrease toxin penetration and increase ribosomal protein synthesis, which, in turn, fuels hepatocyte generation and liver regeneration.[11] Several double-blind, placebo-controlled clinical trials have shown benefit in patients with alcoholic liver disease. Milk thistle significantly decreased liver enzymes and improved histology in 106 Finnish soldiers with alcoholic liver disease over 4 weeks. These results were supported by 2 other trials. However, 2 other trials failed to demonstrate benefit, one possibly because the participants decreased their alcohol intake. Several clinical trials have shown decreased mortality from liver cirrhosis, although results have conflicted. Milk thistle is also beneficial in the treatment of acute and chronic viral hepatitis.[96] No benefit was found against tacrine-induced hepatotoxicity.[97]

The side effect profile for milk thistle extract is low, but it can occasionally have a laxative effect. Like echinacea, milk thistle is a member of the Asteraceae/Compositae family, and should be avoided in patients allergic to other members of this family. Milk thistle may inhibit the cytochrome P450 enzyme 3A4.[20]

Aloe (*Aloe sp.*)
Aloe is best known for its topical use on burns. However, aloe is also used internally. Two different products are derived from aloe. The aloe vera gel comes from the center part of the leaves. The leaf latex comes from the separate cell chambers, which are closer to the outer surface of the leaf. The composition of the two products is dramatically different.[11] The latex contains anthraquinones, which are used as a stimulant laxative. Like other stimulant laxatives, it is unsafe for long-term use. The anthraquinones inhibit resorption of water and electrolytes. As a result, they may cause dependence attributed to potassium loss and the resulting hypomotility and paralysis of the intestine.[2,93] Abdominal cramping and pain may also be present with the other symptoms. Caution should be used in patients in which electrolyte imbalances might jeopardize patient health, such as diuretics, digoxin, hyper/hypokalemia, renal failure, antiarrhythmics, and steroids.

Aloe gel is used internally for inflammation, arthritis, and inflammatory bowel disease (IBD). It must be used with caution because it can be contaminated with aloe latex. Aloe gel is also used topically for burns and injuries, and is, possibly, effective for this purpose. Aloe gel contains carboxypeptidases and salicylates, which may mitigate inflammation and inhibit bradykinin production. Other components may slow the formation of thromboxanes and speed the healing of burns. Magnesium lactate and other principles may decrease itching by inhibiting histamine formation. Aloe may potentiate hypoglycemic agents, so diabetic patients need to monitor blood glucose closely.[2]

Black cohosh
As mounting clinical evidence makes hormone replacement therapy nuances more nebulous, women are searching for perceived "safer" therapies for treating menopausal symptoms. Black cohosh is among the most popular herbs used as a hormone replacement alternative. The active principles are not clearly defined. Although some evidence suggests binding of black cohosh extract to estradiol receptors, the majority of evidence suggests a lack of estrogenic activity.[98] Most clinical trials have used a black cohosh formulation standardized to contain 1 mg triterpene glycosides, calculated as 27-deoxyacetin (Remifemin). Most of the studies have been open-label trials.[2] However, one 12-week, double-blind, placebo-controlled trial found black cohosh to be more effective than estrogen at 0.625 mg daily for relieving menopause-related symptoms of anxiety. Improvement in the vaginal epithelium was more improved in the black cohosh group when compared with estrogen and placebo.[99]

The effects of black cohosh on cardiovascular disease, osteoporosis, or other conditions in postmenopausal women are currently not known. Treatment with black cohosh is not recommended for more than 6 months. In a recent trial of breast cancer survivors who were taking tamoxifen, there was no significant difference in vasomotor symptoms between women taking black cohosh and those taking placebo.[100] However, there is insufficient information on the safety of black cohosh in women with a either history of estrogen-receptor (ER) positive breast cancer or a family history of breast cancer.

CONCLUSIONS
Most of the popular herbs are used for medical conditions that are not easily treated by conventional medicine. Kava kava, St. John's Wort, and valerian are all used for psychiatric

conditions, whereas ginkgo has become popular for memory deficits. Echinacea, goldenseal, garlic, and ginseng are all used to treat infections, notably colds and flu. Milk thistle is used to treat or prevent liver disease. Saw palmetto is used to treat BPH, and black cohosh for menopause. Evidence exists to support further research on most of these herbs. Many occupy spots for which there is no good pharmaceutical equivalent. As regulations and legislation more clearly define dietary supplements, the benefits and risks of using these herbs should become clearer.

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