Herbs Commonly Used by Women:

An Evidence-Based Review

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OBJECTIVE: To review the evidence of herbs commonly used by women.
DATA SOURCES: Articles were located by searching Medline, Cochrane Database of Systemic Reviews, and the Combined Health Information Database and by hand searching the reference lists of recent systematic reviews. The databases were searched in January 2000 and October 2000 by using the Latin and common name of each herb.
METHODS OF STUDY SELECTION: Preference was given to randomized, placebo-controlled trials. When available, English language studies were reviewed. If not, data are presented from review articles that summarize the foreign study.
RESULTS: Many women use herbal therapies. In the United States, herbs are considered dietary supplements. The Food and Drug Administration (FDA) cannot remove them from the market unless they are proven unsafe. The herb industry plans to improve monitoring. Many prospective randomized controlled trials are being funded. Gingko biloba seems to slow the progression of dementia but increases the risk of bleeding. St John's Wort is efficacious for treating mild to moderate depression but has many drug interactions. Ginseng seems to improve well being in perimenopausal women, but it is often impure and has side effects and drug interactions. Garlic slightly lowers blood pressure and lipids. Echinacea slightly decreases the duration of colds but does not prevent them. Valerian is beneficial for insomnia, but there is no long-term safety data. Black cohosh may help the symptoms of perimenopause, and chasteberry may improve premenstrual syndrome. More study is needed on both herbs.
CONCLUSION: Some herbs are medically useful, but the American public would benefit from increased regulation. Manufacturers should be able to ensure that herbs contain pure ingredients. Side effects and drug interactions should be listed. Well-designed studies are being conducted. The results will be helpful to physicians and patients when the clinical evidence becomes available.

Key Words: Phytomedicine, herbal medicine, alternative medicine, herbs

Herbs are everywhere, but most importantly, in your patient's medicine cabinets. Multiple surveys have shown that women (especially white, middle-aged women) are likely to be users of unconventional therapies.[1-3] Herbs are heavily promoted to women for the relief of menstrual difficulties, menopausal symptoms, mood difficulties, and bone health.

The production of herbal medicines in the United States is relatively unregulated. In 1994, republican Senator Orrin Hatch of Utah rushed the Dietary Supplement Health and Education Act (DSHEA) through Congress with the vocal support of the supplement industry in his state and with lobbying by consumers of nutritional supplements.[4] More letters were written in favor of nutritional supplements than were written to protest the Vietnam War.[5] As a result, herbs are marketed as dietary supplements and are not intended to diagnosis, treat, cure, or prevent disease. To be removed from the market, an herb must be proven unsafe and the proof submitted to the Secretary of Health and Human Services. The Food and Drug Administration (FDA) has no authority to test dietary supplements, but can stop the sale of dietary supplements that pose a "significant unreasonable risk of illness or injury" or that make unsubstantiated claims.[5] The FDA had recommended stricter marketing rules regarding structure and function claims. In January 2000, however, their final regulations on structure and function

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claims upheld the original intent of DSHEA. They had received 235,000 public comments supporting DSHEA.

The herbal industry plans to improve monitoring. The American Botanical Council is creating an herbal review board. Many organizations are publishing monographs. The FDA center for drug evaluation is evaluating 48 herbs, and the University of the Sciences in Philadelphia, PA, is forming an institute to set uniform standards for herbs.

There have been concerns about the purity of various herbs. In the United States, some products labeled as ginseng contain mandrake (scopolomine) or snake root (reserpine) because of the high cost of pure ginseng.[6] Herbs have been reported to contain such unlikely additives as steroids, antibiotics, sedatives, narcotics, and nonsteroidal anti-inflammatory drugs.[6-8] Heavy metals have been found in foreign herbal preparations.[9]

Herbs may lack biological chemical standardization and have variable potency. Recently, the *LA Times* had 10 different brands of St John's Wort analyzed for hypericum by mass spectrophotometry. The tested potency ranged from 20% to 140% of claimed potency.[4] Herbal side effects do not have to be listed, and thus many patients believe that herbs are safer than traditional pharmaceuticals.

Therapeutically oriented clinical trials have been the exception, but this is beginning to change. The National Center for Complementary and Alternative Medicine (NCCAM) is sponsoring randomized prospective studies on herbs. In the past, adverse herb reactions were underreported.[10] Recently, major journals have published articles on side effects and drug interactions.[9,11,12] Primary care physicians should specifically ask each patient about their use of herbs, vitamins, or supplements. It is estimated that 20% of Americans use prescription medicines concurrently with herbal remedies.[1]

Unlike the situation in the United States, herbal medicine is regulated in Germany. In 1978, the German government created Commission E, a body in the German Federal Health Agency that reviews scientific studies on each herb. On August 9, 1994, the 5th Amendment to the German Drug Law was passed, stating "scientifically proven phytomedicines will be evaluated for pharmaceutical quality, efficacy, and safety in a normal approval process and given an approval number." There must be absolute proof of safety and "reasonable certainty" of efficacy. Commission E reviews data from clinical trials and historical data.[13] A monograph is issued. These monographs are now available in English for the first time, published by the American Botanical Council.[14]

Despite newly emerging data, physicians remain skeptical of plant-based medicine. Perhaps the lack of known mechanisms of action is part of the reason, along with issues of purity and lack of regulation. Nonetheless, it is important to learn about specific phytomedicines because our patients are using them.

Methods

This clinical review is intended for physicians taking care of women who use herbs. It presents the available evidence regarding the indications, efficacy, drug interactions, and side effects of some of the most commonly used herbs. Articles were found by searching Medline, Cochrane Database of Systematic Reviews, and the Combined Health Information Database (CHID). Also, articles were retrieved by hand searching the reference lists of recent systematic reviews and meta-analyses. When available, placebo-controlled, randomized English language trials were evaluated. If English studies were not available, non-English data were obtained from review articles. The search term used were the Latin and common names of each herb.

Data Synthesis

Ginkgo Biloba. Gingko biloba is a very hardy tree, resistant to insects, microorganisms, and environmental toxins. The first green growth to reappear at the center of Hiroshima in 1946 was the sprout of a gingko tree that grew to be a normal, full-size tree.

The dried green leaves of ginkgo biloba are extracted to manufacture EGb 761. The flavinoid components act as antioxidants, reduce capillary fragility, and increase the threshold of blood loss from capillaries. The ginkolides antagonize platelet-activating factor (PAF), which induces platelet aggregation, degranulation of neutrophils, and production of oxygen radicals.[15] In laboratory animals, antagonism of PAF by ginkolides improves cerebral metabolism and increases cerebral tolerance to hypoxia.[16]

It is approved in Germany for the treatment of cerebral circulatory disturbances that result in reduced functional capacity and vigilance.[14] It is also used to treat peripheral arterial circulatory disturbance. It is the most widely prescribed medicine in Germany with more than 5 million prescriptions written each year. It is the top-selling herb in America with $148 million in sales in 1999.[17]

Kleijnen and Knipschild reviewed 40 controlled clinical trials performed in the 1980s on the use of ginkgo for cerebral insufficiency, which was defined by symptoms such as difficulty concentrating, fatigue, anxiety, dizziness, and headaches. Only 8 trials were of good quality. Seven trials showed positive effects of gingko compared with placebo in symptoms, complaints, and psychometric tests.[18,19]

In America, people (especially perimenopausal women) use gingko to treat age-associated decline in mental function. A study investigated the effects of acute doses of standardized gingko biloba extract on memory and psychomotor performance in 31 healthy volunteers who were aged 30 to 59. The study was randomized, double-blind, placebo-controlled with a 5-way crossover design. Gingko improved working memory in all volunteers but especially in volunteers who were aged 50 to 59.[20]

LeBars et al recently published a 52-week, randomized, double-blind, placebo-controlled, parallel-group multicenter study of 202 mildly to severely demented outpatients with Alzheimer's or multi-infarct dementia, who were given EGb 761 (120 mg/d) or placebo. EGb was safe and stabilized or improved cognitive performance and social functioning for 6 months to a year.[21]

Oken et al conducted a meta-analysis of double-blind, randomized, controlled trials on the use of gingko in dementia if the trial had (1) a clearly defined diagnosis of dementia, (2) clearly stated exclusion criteria, (3) used standardized extracts, and (4) had at least 1 objective assessment of cognitive function. They found 57 studies. Four studies with 424 subjects met these criteria. There was a significant effect size of 0.40 ($P < .0001$).[22]

Ernst and Pittler published a systematic review of double-blind, placebo-controlled trials that evaluated ginkgo biloba extract as a treatment for dementia. They found 9 trials of varying methodological quality that suggest that gingko is more effective than placebo and has few side effects. They recommended further study.[23]

Pittler and Ernst published a meta-analysis of 8 randomized, placebo-controlled, double-blind trials on the use of gingko biloba extract for intermittent claudication. They found that gingko improved pain-free walking distance by 34 meters (95% confidence interval [CI] 26 to 43 meters).[24]

Gingko biloba may be useful in preventing high altitude sickness. Roncin et al recruited 44 people on a Himalayan expedition. Twenty-two people received EGb 761 (80 mg twice daily). None of the treated subjects developed headache compared with 8 placebo subjects. Only 3 treated subjects developed pulmonary symptoms compared with 18 untreated subjects.[25]

At the American Psychiatric Association meeting (San Diego, CA, May 1997), Cohen presented a case series of 37 men and women on selective serotonin reuptake inhibitors (SSRI) with sexual dysfunction, who were previously treated unsuccessfully with cyproheptadine, yobimbine, amantadine, and buspirone hydrochloride. Eighty-six percent reported significant improvement on gingko biloba 60 mg 3 to 4 times daily.[26]

Gingko biloba is considered relatively safe. German postmarketing surveillance of 10,815 patients showed a 1.7% incidence of adverse effects, mostly mild gastrointestinal side effects and headaches.[16] However, gingko toxin (a neurotoxin) may be present. It would be prudent to avoid the use of gingko biloba in epileptic patients because the toxin may decrease the effectiveness of anticonvulsants.[27] Serious bleeding is being increasingly reported, especially in patients on aspirin or warfarin, a result of gingko's ability to inhibit PAF.[28-32]

The dose is 120 to 240 mg each day, 2 to 3 doses per day.

St John's Wort. St John's Wort (SJW) has been used for more than 2,000 years. In 1999, Americans spent $104 million on SJW, making it the second best-selling herb in America.[17] The alcoholic extracts of the SJW flower are atypical antidepressants. Previously, it was speculated that hyericum, the presumed active ingredient, was a weak monoamine oxidase inhibitor (MAOI). This does not seem to be the case in vivo. Hypericum downregulates serotonin receptors, inhibits serotonin reuptake, and antagonizes reserpine. It also inhibits synaptic gamma-aminobutyric acid (GABA) uptake and GABA-receptor binding. It is unable, however, to cross the blood-brain barrier. Hypericum may act by decreasing cytokine production (interleukin-6) in peripheral blood mononuclear cells.[33]

A recent study suggests that hyperforin may be the active ingredient. It inhibits the reuptake of serotinin, dopamine, and norephinephrine and interacts with GABA and glutamate receptors.[34] The effectiveness of SJW correlates with hyperforin content, but not hypericum content.[34-36]

In 1996, Linde et al published a meta-analysis that generated a lot of interest.[37] They updated their meta-analysis in 1999 for the Cochrane Library. It includes 27 randomized trials with 2,291 patients. Seventeen trials with 1,168 patients compared SJW with placebo. There was a 56% response rate with SJW compared with a 26% response rate with placebo. Seventeen trials with 1,123 patients compared SJW with a tricyclic antidepressant (TCA). Pooling of responder rates suggested an equivalent response rate of 1.01 (95% CI 0.87 to 1.16). However, only 50 to 75 mg of imipramine were used, and no trial lasted over 8 weeks.[38]

A systematic review of 8 English language studies with strictly defined depressive criteria found 4 trials comparing SJW with placebo, with an absolute response rate from 23% to 55%. However, the response rates were from 6% to 18% lower when compared with TCAs.[39]

Since 1996, there have been at least 9 randomized trials, all of which confirm the efficacy of SJW.[40] The Remotiv/Imipramine Study Group performed a randomized, multicenter, double-blind, parallel-group trial in 40 outpatient clinics in Germany. The participants were 324 outpatients with mild to moderate depression who were given imipramine (75 mg twice daily) or hypericum extract ZE (117 to 250 mg twice daily) for 6 weeks.

Outcome measures were the Hamilton Depression Rating (HAMD) scale, Clinical Global Impression scale (CGI), and Patients Global Impression scale. The outcomes were similar, except hypericum patients scored better on the anxiety-somatization scale of HAMD. Also, tolerability was better for hypericum (1.67) than imipramine (2.35) on a scale of 1 to 5, with 1 indicating excellent tolerability. Adverse events occurred in 39% of the participants on hypericum and 63% of those on imipramine. Three percent withdrew on hypericum compared with 16% on imipramine.[41]

All of these trials have been of short duration (4 to 8 weeks) and compare SJW with low doses of TCAs. Two re-

cent trials compare SJW and fluoxetine. The first evaluated 161 elderly subjects with mild to moderate depression over 6 weeks. They were treated with SJW (400 mg twice daily) versus fluoxetine (10 mg twice daily). Improvement in HAMD was similar in both groups.[42]

Another randomized, double-blinded, 6-week study funded by German Medical Insurance System compared 240 outpatients taking fluoxetine (20 mg twice daily) or hypericum extract (250 mg twice daily). After 6 weeks, the improvement in the HAMD scores were equivalent. SJW had fewer side effects (28%) than fluoxetine (72%).[43]

Some studies have suggested that SJW may be particularly helpful for patients with somatic symptoms, especially fatigue.[44,45] Martinez et al found that 20 patients with seasonal affective disorder were as responsive to hypericum (900 mg) as to light therapy after 35 days.[46]

The side effects reported in Cochrane's meta-analysis of 2,291 patients found less side effects with SJW than TCAs (26.3% *v* 44.7%).[38] Ernst compiled the adverse effects of SJW in trials: gastrointestinal symptoms (8.5%), dizziness and confusion (4.5%), sedation (4.3%), and dry mouth (4%).[47] Photosensitivity has been a concern after it was reported in cows grazing in fields of SJW.[16] It is rarely reported at therapeutic doses. A case of sun-induced neuropathy has been reported in sun-exposed areas of skin after 4 weeks of hypericum. The symptoms resolved with discontinuation of hypericum.[48] Hypomania, a known complication of other antidepressants, has been reported with SJW.[49-51]

The last 2 years SJW has been in the news repeatedly because of drug interactions. At least 6 cases of serotonin syndrome have been reported when SJW was used with low doses of SSRIs, especially in the elderly.[52-54] SJW induces hepatic cytochrome p 450, enzymes 3A4 and 2C9, and also induces the gut p–glycoprotein transporter[55] decreasing the levels of many drugs including digoxin,[56] cyclosporin,[57] indinavir,[58] warfarin,[59] estrogen,[59] and theophylline.[60-62]

After a report in the Lancet of reduction of indinavir levels by SJW, the FDA issued a health advisory warning against the concomitant use of SJW with human immunodeficiency virus (HIV) protease inhibitors and possibly other similarly metabolized drugs. In response, several countries including Japan, the United Kingdom, and Canada restricted sales and regulated labeling. The French Health Ministry banned the sale of all food products and supplements containing SJW.[63]

SJW seems to be effective for mild to moderate depression with less side effects than TCAs. However, there have been no long-term trials and no large trials comparing SJW with SSRIs. Also, there are many drug interactions. Currently, there are several ongoing national trials of SJW.[64-66]

Ginseng. Ginseng is the third most popular herbal product in America, with $84 million in sales in 1999.[17] It has been used in Asia for over 2,000 years and has the most extensive body of scientific literature of any medicinal herb. Ginseng is also known as man-root because the shape of the root resembles a human being. It is believed to benefit all aspects of the human body. Its scientific name, Panax ginseng, alludes to its purported panacea-like quality.[67] In Chinese medicine, ginseng is used as an adaptogen to increase the body's resistance to physical, chemical, and biological stress. It is used to treat symptoms of anxiety, weakness, dyspnea, forgetfulness, fatigue, decreased libido, and nausea.[68] It was approved by Commission E in 1981 as a tonic to counteract weakness and fatigue, a restorative for declining stamina and impaired concentration, and as an aid to convalescence.[14] Today, people use ginseng to enhance physical performance and to improve vitality, immune function, sexual function, and fertility. It is used to treat type 2 diabetes, HIV, cancer, and hyperlipidemia.[69]

The major active components of ginseng are at least 18 ginsenosides, a diverse group of steroidal saponins, that show the ability to target a myriad of tissues, producing a variety of pharmacological responses. Many mechanisms of ginsenoside activity still remain unknown. Because ginsenosides and other constituents of ginseng produce effects that are different from each another, the overall pharmacology of ginseng is complex.[69] Ginsenosides scavenge free radicals, possess calcium channel blocking activity, increase insulin, slightly decrease glucose, have a mild estrogen effect, and are functional ligands of the glucocorticoid receptor.

There are several plant types: Asian (red, Panax ginseng), American (white, Panax quinquefolium), Japanese (Panax japonicus), Sanchi (Panax notoginseng), and Siberian (Eleutherococcus senticosus). Each has different chemical constituents and different properties.[70] Siberian ginseng is in a different genus and is not a true ginseng. Vogler et al performed a systematic review of double-blind, placebo-controlled trials of ginseng root for any indication in any language. They searched multiple databases and contacted manufacturers and experts. They located 16 trials related to physical performance, psychomotor performance, cognitive function, immunomodulation, diabetes mellitus, and herpes simplex type II infection. They concluded that the evidence was not compelling for any of these indications.[71]

Another review on the potential efficacy of ginseng use for enhancing physical performance in humans concluded that there is a lack of compelling research evidence about the use of ginseng to improve physical performance.[72] Another review found that controlled studies of Asian ginseng showed improvements when standardized root extracts were used. The study lasted longer than 8 weeks, the daily dose was greater than 1 gram of dried root, and there were a large number of subjects and older subjects.[73]

A double-blind, placebo-controlled multicenter study of 36 newly diagnosed type 2 diabetics who were given ginseng (100 mg and 200 mg four times daily) or placebo for 8 weeks showed that the patients given ginseng 200 mg had significantly reduced HbA1C and improved mood. There was no change in lipid profiles.[74] A small preliminary controlled study showed that American ginseng attenuated postprandial glycemia in 10 nondiabetics and 9 diabetics.[75] The mechanism seems to be inhibition of sugar absorption in the small intestine.[76]

Women, particularly perimenopausal women, take ginseng to help fatigue and improve their sense of well-being.[77] The literature on the use of ginseng for fatigue is conflicting and inconclusive.[72] However, a recent randomized, multicenter, double-blind, parallel-group study performed in 284 perimenopausal women found that treated women reported less depression and improved well-being ($P < .05$). The effects were measured with validated questionnaires. Ginseng had no effect on hormonal parameters.[78] A Japanese study in 20 postmenopausal women found that women with climacteric syndromes (n = 12) of fatigue, insomnia, and depression had lower dehydroepiandrosterone sulfate (DHEA-S) levels than women without climacteric syndromes (n = 8). Daily treatment with 6 grams of red ginseng for 30 days improved DHEA-S levels and psychological symptoms.[79]

There have been numerous studies on ginseng's ability to prevent cancer. Cellular studies have found that Panax ginseng inhibits multiple cancer cell lines. Animal studies show a reduction in cancer incidence.[80] In humans, results from a cohort study and 2 case-controlled studies in Korea showed that patients using ginseng had a significant decreased risk for cancer of the respiratory tract, gastrointestinal tract, liver, pancreas, and ovaries. There seemed to be a dose-response relationship.[77,81,82] A review on the cancer-preventative potential of ginseng concluded that further research is warranted.[80]

There have been reports of vaginal bleeding and mastalgia in women.[83-87] Ginseng has been associated with agitation in a schizophrenic patient and mania in a depressed patient.[88,89] Hypertension, euphoria, nervousness, insomnia, rash, and diarrhea have been reported in 14 of 133 patients using an average dose of 3 grams of ginseng root daily.[90]

Ginseng should be avoided in patients with hypertension, emotional imbalance, headaches, heart palpitations, insomnia, asthma, and high fever. Also, pregnant women should avoid ginseng because of hormonal effects, and children should avoid taking ginseng because of stimulant effects.[90]

Siberian ginseng has been associated with a falsely elevated serum digoxin level because of interference with the assay.[91] Ginseng may decrease the international normalized ratio (INR) in patients on warfarin, and it may interfere with phenelzine.[92,93]

Panax ginseng is very expensive, and commercial preparations vary tremendously in quality.[94] One analysis of the quality of 54 available ginseng products found that 85% contained little or no ginseng.[95] Some ginseng products in America contain a high percentage of alcohol, and some have been contaminated with geranium.[94] Also, Siberian ginseng (Eluetherococcus senticosus) contains no true ginseng.

Ginseng is marketed in many forms such as slices, tonics, powders, tablets, teas, extracts, confectioners, fruit, and mineral drinks. The dose is 1 to 2 grams of crude herb daily or 100 to 300 mg of ginseng extract 3 times a day.

Garlic. Garlic is a traditional medicinal herb used in Sumeria, Egypt, Israel, China, and Europe. Historically, garlic was used in China to lower blood pressure, in Egypt to increase physical strength, and in Europe to prevent plague.[67] Today, it is used as an antiplatelet, antiparasitic, antifungal, antiviral, anti-inflammatory, and anticancer agent by patients. Its reputed anti-infectious, antitumor, and antioxidant properties will not be reviewed here but have been reviewed elsewhere.[96]

Garlic is approved by Commission E to support dietary measures in the treatment of hyperlipidemia and to prevent age-related changes in blood vessels.[14] Many postmenopausal women realize they are at risk for cardiovascular disease and use garlic to decrease their cholesterol and prevent atherosclerosis.

Garlic contains sulfur-rich derivatives of the amino acid cysteine-alliin. When raw garlic is cut or crushed, the enzyme allinase interacts with the cysteine compound alliin to produce allicin, which gives the garlic aroma and is thought to be medicinal. Allicin breaks down after a few hours at room temperature or after 20 minutes of cooking. Garlic may inhibit hepatic hydroxymethylglutaryl coenzyme A (MHG Co A) reductace.[97] Garlic also activates fibrinolysis and inhibits platelet activation.[98,99]

Animal in vitro and ex vivo studies suggest inhibition of lipid uptake by aortic cells, inhibition of smooth muscle proliferation, and decreased oxidation of low-density lipoprotein (LDL). Koscielny followed 280 patients with advanced atherosclerotic plaques as measured by ultrasound in the carotid or femoral artery and at least 1 cardiac risk factor. They were assigned to treatment with 900 mg of garlic powder per day or placebo and were followed for 48 months. There was a significant difference in plaque volume of 18.3% after 4 years, suggesting that garlic may have a role in the treatment of arteriosclerosis.[100]

Many small clinical trials have reported that garlic lowers cholesterol. Two recent meta-analyses showed an average reduction of 9% to 12% in total cholesterol and 13% in triglycerides.[101,102] Three randomized, double-blind, placebo-controlled trials show an even more modest effect of a 6.1% to 11.5% reduction in LDL cholesterol.[103-105] Five additional studies have failed to show any

significant cholesterol-lowering benefit on lipid levels.[106-110] This discrepancy may be explained by differences in formulations. Only fresh garlic has a significant amount of allicin.[111]

A meta-analysis of 13 trials concluded that garlic is superior to placebo in reducing total cholesterol. The effect is modest, however, and the 6 diet-controlled trials with the highest score for methodologic quality did not show a significant difference between garlic and placebo.[112]

Garlic has only a weak antihypertensive effect. Meta-analysis of 8 studies showed a significant reduction of diastolic blood pressure in 4 studies and systolic blood pressure in 3 studies.[113] Several small, nondefinitive randomized clinical trials also support garlic's antiplatelet, antithrombotic, and fibrinolytic properties.[114]

The reported side effects have been mild but include gastrointestinal discomfort, bloating, headache, sweating, lightheadedness, menorrhagia, and of course, garlic odor.[16] Rarely, garlic causes contact dermatitis, asthma, and even anaphylaxis.[115,116] Caution should be exercised with other agents that have antiplatelet effects such as aspirin, ginkgo, feverfew, and nonsteroidal anti-inflammatory drugs (NSAID). Garlic may increase the INR in patients on warfarin.[117] Garlic has been associated with postoperative bleeding and a spontaneous spinal epidural hematoma in an 87-year-old man.[118-120]

The dose is .6 to 1.2 grams of dried powder or 2 to 4 grams of fresh garlic daily (about 1 clove) or enteric coated tablets, 300 mg 2 to 3 times per day.

Echinacea. Echinacea or purple coneflower is a member of the daisy family. It is the alcoholic extract made from the root of the narrow-leafed coneflower (echinacea pallida) or juices from fresh parts of the purple coneflower (echinacea purpurea). It has been used for centuries by Native Americans for chest colds, sores, and as an antiseptic and analgesic. One hundred years ago, it was the best selling native medicinal plant in America.[121] With the advent of antibiotics, echinacea was used rarely until the early 1990s when 2 clinical trials in Germany found that it decreased the length and severity of the common cold.[122,123] In 1999, it was the fifth most popular herb in the United States with $70 million in sales.[17]

Commission E has approved echinacea for internal use in supportive therapy of upper respiratory tract (URI) and lower urinary tract infections and for external use on hard-to-heal superficial wounds and ulcers.[14]

Echinacea is a nonspecific immunostimulant. The caffeic acid derivatives increase phagocytosis and stimulate the production of interferon, interleukins, and tumor necrosis factor. The polysaccharides, such as insulin, stimulate macrophages and inhibit hyaluronidase activity to decrease inflammation. Alkylamides have a local anesthetic effect and inhibit hyaluronidase activity.[124] Echinacea has little direct bactericidal or bacteriostatic properties. It has mild antiviral activity.[125]

An earlier meta-analysis of 26 controlled trials (18 randomized, 11 double-blind) tested the efficiency of echinacea in the common cold. Positive results were claimed for 88% of treated groups. Most trials were of poor methodologic quality.[126] Three recent studies have had negative results—2 prevention and 1 treatment trial.[127-129]

In a well-designed study, volunteers from the Medical University of South Carolina were recruited to receive exposure to rhinovoris type 23. After the virus challenge, 117 subjects received echinacea or placebo for 5 days. The echinacea preparation was standardized to contain 0.16% cichoric acid, but minute amounts of echinacosides and alkamides. There were no significant differences between groups in incidence of rhinovirus infection or cold symptoms of severity of symptoms.[130]

A Swedish randomized, double-blind, placebo-controlled study recruited 5,519 healthy adult volunteers. When 246 adults developed cold symptoms, they were given echinaforce (95% herbs, 5% radix), echinacea purpurea concentrate, echinacea purpurea radix, or placebo for up to 7 days. The primary end point was a reduction in the complaint index defined by 12 cold symptoms. Echinaforce and its concentrated form reduced the complaint index 62.7% and 64.3% compared with echinacea radix (44.8%) and placebo (29.3%).[131]

Barrett et al published an evidence-based clinical review of echinacea for URI. They included published and unpublished reports of all blinded, placebo-controlled, randomized trials of any echinacea formulation in the treatment or prevention of URIs. They reviewed 9 treatment and 4 prevention trials. Eight of 9 treatment trials showed benefits, whereas only 2 of 4 prevention trials showed marginal benefit. They found that echinacea preparations vary widely in composition and are often used in combination with other potential active constituents.[132] These results agree with another recent overview of 26 sources of data that concluded that echinacea is effective in reducing the duration and severity of symptoms, but that this effect is noted only with certain preparations of echinacea.[133] Preparations vary according to plant species, plant components, and processing and application methods.[14] NCCAM has recommended that further testing be done with echinacea because it shows promise for the treatment of URIs.[134]

Echinacea is a member of the asteracae family, which contains ragweed and yarrow. Patients with ragweed allergies may have immunoglobulin E (IgE)-mediated allergic reactions, including anaphylaxis.[135-137]

Reported side effects include gastrointestinal upset, diarrhea and constipation, and skin rash. Because hepatotoxic effects may be associated with persistent use, it should not be taken with other known hepatotoxic drugs.[11] The German government advised people with impaired immunity to avoid immunostimulants, including echinacea.[14] This contraindication is theoretical and

not well documented. There are no known drug interactions. Echinacea should be started at the first onset of symptoms and taken for 10 to 14 days.

Valerian. Valerian has been used for centuries by the Greeks, Romans, Chinese, American Indians, and Europeans. It was dropped from the US National Formulary with the introduction of barbiturates. The extract of the malodorous root of valerian officinales was approved by Commission E in 1985 for states of unrest and nervous sleep disturbance.[14]

The active component is not well characterized. Both valeprotriates and volatile oils have been reported to prolong barbiturate-induced sleep time in rodents. Valerenic acid 52 exerts pentobarbital-like central depressant activity. Some valepotriates have antidepressant properties. Valerian has hypotensive, anticonvulsive sedative, and hypnotic effects.[138] It increases the secretion of GABA and inhibits its uptake.[139] It binds the same receptors as benzodiazepines but with less efficiency and milder effects.[140]

In 2 randomized, blind, placebo-controlled, crossover trials (n= 128, n = 8), valerian (400 to 450 mg) resulted in significantly improved subjective sleep quality and decreased sleep latency with no residual morning sedation. The second study compared valerian 450 mg with 900 mg. The higher dose offered no advantage.[141,142]

A more recent German study randomized 121 patients with insomnia (ICD-10) to valerian 600 mg (standardized to 0.4% to 0.6% valerenic acid) or placebo. The outcome measures were 2 sleep questionnaires, 1 mood scale, and CGI. By 2 weeks, 2 of 4 scales improved, and by 4 weeks, 4 of 4 scales improved.[143] NCCAM has recommended further study of valerian for insomnia.[134]

The side effects include headache, hangover, paradoxical stimulation, restlessness, and cardiac disturbances. Overdose causes ataxia, hypothermia, decreased sensibility, hallucinations, and increased muscle relaxation.[144]

No drug interactions were reported by Commission E, but theoretically valerian could potentiate the effect of barbiturates, benzodiazepines, opiates, and alcohol.[145,146] It prolongs thiopental- and pentobarbital-induced sleep.[146] Patients should avoid driving or operating machinery after taking valerian. Some components display cytotoxic and mutagenic activity in vitro. Valerian should not be used in pregnancy. The dose is 450 mg at bedtime.

Black Cohosh. Cimifuga racemosa is a member of the buttercup family. It is native to eastern North America, growing in moist or dry woods. It is a hardy perennial that grows 9 feet with beautiful flowers. The supplement comes from the root. The Latin name means cimex-bug fugare—put to flight. It was used as an insect repellant.[147] It was known as squawroot by American Indians and used to treat female complaints, snake bites, and as an insect repellant.[148] It was used by American and European folk herbalists to treat female complaints and rheumatism.[149] Black cohosh was part of Lydia E. Pinkham's vegetable compound used by turn-of-the-century women to ease "all those painful complaints and weaknesses so common to our best female population."[150] It was also considered useful by eclectic physicians who practiced herbal medicine until the early 20th century.[151] In more recent times, it has been approved by the Commission E for painful menstruation and menopausal symptoms.[14]

Black cohosh contains triterpene glycosides. The mechanism of action is unclear. It may bind estrogen receptors.[152] Although animal studies show suppression of luteinizing hormone (LH), human data are inconsistent, with 1 study showing no change and another showing suppression.[152-154] Studies on black cohosh's effect on proliferation of breast cancer cell lines are also inconsistent.[155-159]

Black cohosh is the most promising herbal remedy for hot flashes, mood swings, and vaginal dryness.[160] Although it is the most studied of the phytoestrogenic herbs, the existing studies are neither controlled nor randomized, are small and brief, and include subjects of heterogeneous or undefined estrogen status.[151] The majority of studies are German and use Remifemin (Schaper and Brümmer Gmb M & Company, Salzgitter-Ringelheim, Germany), a commercial isopronpanolic extract of black cohosh. A series of open clinical studies in more than 800 women show a reduction in hot flashes, an improvement in global menopausal symptoms, and stimulation of vaginal maturation with little or no toxicity.[161-165] A recent review of 8 German studies written by an employee of the manufacturer of Remifemin concludes that the extract is both safe and effective in alleviating the symptoms of menopause.[166]

In 1987, a 12-week, randomized, double-blind study in 80 women compared Remifemin (2 tablets twice daily) with conjugated estrogens (0.625 mg) or placebo. The Kupperman menopausal index and Hamilton anxiety scale improved equally on Remifemin and estrogen. No improvement was seen with placebo. Interestingly, black cohosh caused a greater increase in vaginal epithelial proliferation than estrogen.[167]

Black cohosh is also used for dysmenorrhea and to augment labor.[168,169] Although black cohosh is approved by Commission E for dysmenorrhea,[14] there are no studies using black cohosh for dysmenorrhea in English peer-reviewed literature.

The most commonly reported side effects are mild gastric complaints. High doses cause headaches, vomiting, and dizziness. Black cohosh is contraindicated in aspirin sensitivity because it contains salicylates.[160] There have been no documented herb-drug interactions.[168] It is not recommended for those who are pregnant or breast feeding because of a lack of data. Its use is not recommended for more than 6 months because of a lack of long-term data.[14] The

dose of Remifemin is 20 mg twice daily. Fortunately, better data may be available soon because the University of Illinois has a $7.9 million grant to study the 10 most popular herbal supplements, including black cohosh.[150]

Chasteberry Tree Berry (Vitex). The dried ripe fruit of the chaste tree, Vitex (agnus-castus L), has been used for female reproductive complaints since ancient Greece.[170] In medevial times, it was used to decrease sexual desire in men, thus the name chaste tree or monk's pepper.[171] In Germany, Vitex has a long history of use and is approved by Commission E for the treatment of menstrual irregularities and premenstrual syndrome (PMS).[14]

The active ingredients are 2, ridoid glycosides-agnuside (0.6%) and aucubin (0.3%), flavonoids, and essentials oils.[172,173] Animal and human studies show that extracts of chasteberry tree berry bind dopamine receptors in the anterior pituitary and decrease both the basal- and thyrotropin-releasing–hormone stimulated secretion of prolactin.[174,175] Women with PMS have significantly higher levels of prolactin, especially in the second and third week of their cycles.[176] Some researchers postulate that vitex causes a decrease in prolactin which leads to reversal of LH suppression allowing full development of the corpus luteum in the luteal phase and increased progrestone levels with decreased premenstrual symptoms.[177,178] The pooled results of controlled German drug monitoring studies in patients show good response rates, with less than 2% of women reporting mild side effects.[179]

A double-blind, randomized trial in 175 women with PMS compared Vitex (3.5 to 4.2 mg 4 times daily) to pyrodoxine (100 mg twice daily for the second half of the menstrual cycle). Placebo was used the first 2 weeks in place of pyrodoxine. There was no placebo arm. After 3 menstrual cycles, 126 patients were evaluated with the Premenstrual Tension Scale and the CGI scale. Efficacy on CGI scores was rated at 77.1% for Vitex and 60.6% for pyridoxine. Adverse effects were minor. The 20 women who discontinued treatment were not included in the analyses.[180]

Side effects seem to be minor and include gastrointestinal complaints, mild skin rash, increased acne, headaches, and increased menstrual flow.[179] There is 1 case report of mild ovarian hyperstimulation documented by ultrasound in a women undergoing unstimulated in vitro fertilization.[181] Chaste tree berry should not be used during pregnancy or while lactating because of a lack of data. There are no reported drug interactions, but theoretically, Vitex may counteract the effectiveness of birth control pills by its effect on prolactin.[182] Vitex is a dopamine agonist, therefore theoretically it could interact with other dopamine agonists or antagonists.[182] The dose depends on the formulation.[184]

Conclusion

Some herbs are medically useful. Gingko biloba seems to be more effective than placebo for dementia and may help working memory in older individuals. However, it inhibits platelet activating factor and has been associated with serious bleeding, especially in patients on aspirin or warfarin. Consistently, short-term studies have shown SJW to be effective for mild to moderate depression. It has few side effects but many drug interactions, and therefore caution is advised. Ginseng does not seem to improve short-term physical performance, cognitive function, or aid in immunomodulation. However, it may attenuate postprandial glycemia and help psychological symptoms in perimenopausal women. Case-controlled studies suggest a decreased risk for certain cancers in people who regularly use ginseng. In America, ginseng is often impure and has been associated with side effects.

Garlic is associated with very modest reductions in cholesterol and has a weak antihypertensive effects. Studies suggest that it may decrease atherosclerotic plaque. Only fresh garlic is active. It cannot be recommended as a treatment for hyperlipidemia or hypertension, but it is recommended as a healthy, flavorful addition to a plant-based diet. Echinacea is probably effective in reducing the duration and severity of upper respiratory symptoms, but it does not prevent infection. It may cause allergic reactions, especially in people allergic to ragweed.

Valerian may help patients with insomnia, but long-term safety is not established. Black cohosh may help hot flashes, mood swings, and vaginal dryness in perimenopausal women. There are no data on long-term safety. Chasteberry may improve premenstrual syndrome, but again more study is needed.

Many patients use dietary supplements in conjunction with traditional pharmaceuticals often for the same health conditions.[1] Drug interactions can occur. It is very important to routinely ask all new patients and all patients with a new symptom if they are using herbs, vitamins, or dietary supplements.

The American public would benefit from increased regulation of the herbal industry. Manufacturers should be able to ensure that herbs contain pure ingredients. Side effects and drug interactions should be listed. Fortunately, well-designed studies are being conducted. The results will be helpful to physicians and patients.

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