The Risk–Benefit Profile of Commonly Used Herbal Therapies: Ginkgo, St. John's Wort, Ginseng, Echinacea, Saw Palmetto, and Kava

Edzard Ernst, MD, PhD, FRCP(Edin)

Because use of herbal remedies is increasing, a risk–benefit profile of commonly used herbs is needed. This article provides a clinically oriented overview of the efficacy and safety of ginkgo, St. John's wort, ginseng, echinacea, saw palmetto, and kava. Wherever possible, assessments are based on systematic reviews of randomized clinical trials. Encouraging data support the efficacy of some of these popular herbal medicinal products, and the potential for doing good seems greater than that for doing harm. The published evidence suggests that ginkgo is of questionable use for memory loss and tinnitus but has some effect on dementia and intermittent claudication. St. John's wort is efficacious for mild to moderate depression, but serious concerns exist about its interactions with several conventional drugs. Well-conducted clinical trials do not support the efficacy of ginseng to treat any condition. Echinacea may be helpful in the treatment or prevention of upper respiratory tract infections, but trial data are not fully convincing. Saw palmetto has been shown in short-term trials to be efficacious in reducing the symptoms of benign prostatic hyperplasia. Kava is an efficacious short-term treatment for anxiety. None of these herbal medicines is free of adverse effects. Because the evidence is incomplete, risk–benefit assessments are not completely reliable, and much knowledge is still lacking.

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For the author affiliation and current address, see end of text.

Physicians' need for reliable information on herbal medicinal products is considerable. In the United States, the popularity of complementary and alternative medicine is growing at a remarkable and perhaps disquieting speed (1). Herbal medicine has grown faster than any other "alternative" treatment method in the United States (1, 2). The seven top-selling herbal medicinal products in the United States are *Ginkgo biloba* (total 1998 retail sales of $151 million), St. John's wort ($140 million), ginseng ($96 million), garlic ($84 million), echinacea ($70 million), saw palmetto ($32 million), and kava ($17 million) (3). (Garlic is not discussed in this article; the reader is referred to two recent meta-analyses [4, 5].)

Physicians regularly see patients who self-prescribe herbal medicinal products but do not volunteer this information (1). Many herbal medicines have adverse effects, and most can interact with purified prescription drugs (6). A complete medical history should therefore include specific questions about the use of herbal medicinal products (7), and physicians must acquire sufficient knowledge in this area to advise their patients responsibly.

This article provides risk–benefit profiles for the most commonly used herbal medicines. These profiles are based on systematic reviews where possible.

METHODS

Electronic literature searches were done to locate all systematic reviews of gingko, St. John's wort, ginseng, echinacea, saw palmetto, and kava. The MEDLINE (via PubMed), EMBASE, CISCOM, and AMED databases and the Cochrane Library were searched from their inception to October 2000. In addition, nine experts in the field were asked for further details on systematic reviews, and the author's personal files were searched for further articles.

All systematic reviews of randomized clinical trials in humans were included. They were read in full, and key data were extracted according to criteria that appear as column headers in **Table 1**. The quality of the reviews was estimated according to the guidelines of the Quality of Reporting of Meta-analyses statement (23). In essence, the following questions were asked: Are the objectives of the review clearly stated? Are the data sources stated? Are the search methods explained? Are inclusion and exclusion criteria stated? Was the validity of primary data assessed? Is the data abstraction process explained? Were the study characteristics assessed? Are the results adequately discussed? If the answer to seven or more of these nine questions was "yes," the review was rated as "good"; if four to six responses were positive, it was rated as "adequate"; and if three or fewer were positive, it was rated as "poor." Of note, the methodologic quality of a systematic review and that of the primary studies are largely independent: For example, weak clinical trials can be analyzed in a high-quality review.

GINKGO (*GINKGO BILOBA*)

Ginkgo fruits and seeds have been used in traditional Chinese medicine for millennia (mostly to treat

asthma and chilblains). The flavonoids and terpene lactones from the ginkgo leaf, which today is used for medicinal purposes, are associated with diverse pharmacologic actions (**Table 2**). In vitro and in vivo studies suggest that ginkgo has antiedemic, antihypoxic, free radical–scavenging, antioxidant, metabolic, antiplatelet, hemorheologic, and microcirculatory actions (8, 24). Ginkgo has been used experimentally for myocardial reperfusion injury, depression, brain trauma, free radical damage to the retina, cochlea deafness, vertigo, male impotence, and asthma (9). In clinical practice, it is used mostly for memory impairment, dementia, tinnitus, and intermittent claudication. In some European countries, ginkgo is registered for these indications; in the United States, it is marketed as a dietary supplement.

Memory Impairment

A rigorous systematic review of high methodologic quality included 40 mostly weak controlled trials of ginkgo for "cerebral insufficiency": memory impairment but not dementia (10). With their own scoring system, the authors judged that only 8 of the primary studies had good methodologic quality. All but 1 of these 8 studies showed positive effects of ginkgo on cognitive function compared with placebo. For global effectiveness ratings and single symptoms (such as forgetfulness), clear evidence favored ginkgo over placebo. However, the authors warn of publication bias because "there were no negative results reported in many trials of low quality" (10). Another, less rigorous meta-analysis studied one standardized extract (11). The author did not formally assess the quality of the primary studies. Of the 11 randomized clinical trials included, 5 had not been included in the previous meta-analysis (10). Again, the conclusions were positive (**Table 1**).

Thus, encouraging data exist, but the evidence for ginkgo as a memory enhancer is not fully convincing. Contrary to claims often made, no compelling evidence shows that ginkgo enhances normal cognitive function.

Dementia

A systematic review of adequate quality (25) included nine randomized, double-blind, placebo-controlled clinical trials of ginkgo to treat dementia. Methodologic quality of the primary studies was assessed by using the Jadad score, and three studies had the highest possible rating (5 out of 5 points). Eight studies, including the three highest-quality studies, suggested that ginkgo is significantly more effective than placebo in delaying clinical cognitive deterioration in dementia.

Using stricter entry criteria, Oken and colleagues (12) conducted a meta-analysis of high methodologic quality of four randomized, double-blind, placebo-controlled clinical trials of ginkgo to treat Alzheimer disease. All of these studies were included in our analysis (25). The methodologic quality of the primary studies was not formally assessed. Again, the overall result was positive. The pooled effect size in terms of cognitive function was moderate and translated into a 3% difference in the Alzheimer's Disease Assessment Scale–Cognitive subtest (**Table 1**). Thus, the average effect size associated with ginkgo is likely to be clinically relevant.

Tinnitus

Ginkgo increases fluidity of blood and thus might optimize blood flow at the microcirculatory level (13). These effects prompted testing the clinical efficacy of ginkgo in treating tinnitus. A systematic review of adequate quality (26) summarized all five randomized clinical trials of ginkgo for this indication (**Table 1**). Methodologic quality of the primary studies was assessed by using the Jadad score, and only one study was deemed to be of sufficient rigor. The results showed a moderate but statistically significant effect of ginkgo extract taken for 12 weeks on the perceived loudness of the tinnitus sound. Because few rigorous trials have been published, the therapeutic value of ginkgo for tinnitus is uncertain.

Intermittent Claudication

Because gingko may optimize microcirculatory blood flow, it has been used to treat intermittent claudication. A meta-analysis of good quality (27) pooled results of eight randomized, double-blind, placebo-controlled clinical trials and calculated the weighted mean difference in pain-free walking distance between the experimental and control groups (**Table 1**). The methodologic quality of the primary data was assessed by using the Jadad score, and most studies received 5 or 4 points out of the maximum of 5. The results indicate that gingko recipients walked 34 m (95% CI, 26 to 43 m) farther without pain compared with controls. Thus, the effect is moderate yet probably clinically relevant.

Comparative studies of ginkgo and pentoxifylline

Table 1. **Systematic Reviews of Top-Selling Herbal Medicinal Products***

Common Name (Manufacturer)†	Indication	Type of Study (Quality Estimate)	Trials (Patients), *n (n)*	Average Methodologic Quality‡
Ginkgo (Schwabe, Lichtwer)	Memory impairment	Qualitative systematic review (good)	40 (not mentioned)	Only 8 trials were good
		Meta-analysis (adequate)	11 (11 130)	Good, but not formally evaluated
	Dementia	Qualitative systematic review (good)	9 (1497)	Good
		Meta-analysis (adequate)	4 (212)	Good, but not formally evaluated
	Tinnitus	Qualitative systematic review (adequate)	5 (621)	Poor
	Intermittent claudication	Meta-analysis (good)	8 (413)	Very good
St. John's wort (Lichtwer)	Mild to moderate depression I	Meta-analysis (good)	23 (1757)	Good
	Depression	Qualitative systematic review (adequate)	6 (881)	Very good
		Qualitative systematic review (good)	8 (985)	Very good, but not formally evaluated
		Qualitative systematic review and meta-analysis (good)	6 (651)	Very good, but not formally evaluated
	Multiple depressive disorders	Meta-analysis (good)	14 (1417)	Very good, but not formally evaluated
Ginseng (Asian) (Pharmaton)	Various	Qualitative systematic review (adequate)	16 (NA)	Mostly poor
Echinacea (Madaus)	Prevention and treatment of upper respiratory tract infection	Qualitative systematic review (good)	16 (3396)	Moderate to good
Saw palmetto (Schwabe)	Benign prostatic hyperplasia	Meta-analysis (good)	18 (2939)	Good
Kava (Schwabe)	Anxiety	Meta-analysis (adequate)	7 (377)	Good

* NA = not applicable.
† The manufacturers listed are those that make herbal medicinal products frequently tested in clinical trials. Their locations are as follows: Schwabe: Karlsruhe, Germany; Lichtwer: Berlin, Germany; Pharmaton: Lugano, Switzerland; and Madaus: Cologne, Germany.
‡ Quality of primary studies, as estimated by the authors of the review (different methods were used).

(the gold standard treatment in Europe for intermittent claudication) suggest that both treatments are similarly effective in increasing the walking distance of patients with claudication (28, 29). However, compared with regular walking exercises, ginkgo is clearly less effective (30).

Safety

Adverse effects of ginkgo are usually mild, transient, and reversible (**Table 3**). Potentially serious adverse effects are bleeding (for example, subdural hematoma) (8, 24) and seizures, which were seen in children after excessive ingestion of seeds (31). Because gingko has antiplatelet activity (6), it may interact with anticoagulants (31, 32); several cases have been reported (14).

Dosage

Adequate dose-finding studies for gingko are not available. Clinical experience and data from randomized clinical trials suggest the therapeutic window is wide. Clinical trials used dosages of 120 to 320 mg/d. The most common dosage is 40 mg of standardized extract of ginkgo leaf thrice daily (24). Quality extracts are characterized by 22% to 27% flavone glycosides and 5% to 7% terpin lactones (2.8% to 3.4% ginkgolides and 2.6% to 3.6% bilobalides) (15). Clinical effects usually emerge after about 4 weeks of treatment. Use of low-quality, nonstandardized extracts should be discouraged.

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

St. John's wort, applied topically or systemically, has been used to treat bronchitis, burns, cancer, enuresis, gastritis, hemorrhoids, hypothyroidism, insect bites, insomnia, kidney disease, scabies, and wound healing (31). Today, it is used almost exclusively as an herbal antidepressant. Its mechanism of action is now thought

Table 1—**Continued**

Main Result or Conclusion	Comment	Reference
Ginkgo is superior to placebo, but with caveats	Possible publication bias	8
Ginkgo is superior to placebo	The largest study was not randomized	9
Ginkgo is convincingly superior to placebo	Large variation in dosages used	10
Mean effect size, 0.41 (95% CI, 0.22–0.61)	Effect size equals about 1 SD	11
4 trials were positive (including the most rigorous study)	No firm conclusions because of lack of rigorous trials	12
Average increase in pain-free walking distance, 36.3 m (95% CI, 0.9–1.3 m) compared with reference medications	Effect size is moderate but compares well with those of other oral medications for this condition	13
Odds ratio, 2.5 (95% CI, 1.7–3.6) vs. placebo and 1.1 (95% CI, 0.9–1.2) vs. reference medications	Reference medications were underdosed in several of the comparative trials	14
All placebo-controlled trials favored St. John's wort	One trial also suggested efficacy in severe depression	15
All placebo-controlled trials favored St. John's wort	Review also included 1 positive trial in severe depression	16
Relative risk, 1.48 (95% CI, 1.03–1.92) in favor of St. John's wort	Authors criticized the short duration of studies	17
Relative benefit of 1.9 over placebo and 1.2 over tricyclic antidepressants	6 studies on major depression were included; possible publication bias	18
No indication is supported by compelling evidence	Epidemiologic data suggest that regular intake may minimize cancer risk	19
Some preparations have a better effect than placebo	Considerable lack of uniformity among studies; possible publication bias	20
Superior to placebo and equivalent to finasteride	No long-term data available	21
Weighted mean difference in Hamilton Anxiety Scale score of 9.7 (95% CI, 3.5–15.8)	Only symptomatic therapy, and only short-term	22

to lie in selective inhibition of serotonin, dopamine, and norepinephrine reuptake in the central nervous system (15). St. John's wort contains various potentially active compounds; hypericin and hyperforin are thought to be its main active constituents (15) (**Table 2**).

Efficacy

A meta-analysis of good methodologic quality included 27 randomized, double-blind clinical trials (16). The authors used the Jadad score to evaluate the methodologic quality of the primary studies and found their average quality to be good. Seventeen trials were placebo-controlled and showed efficacy of St. John's wort in mild to moderate depression. Ten compared St. John's wort extracts with standard reference medications and showed apparent equivalence to maprotiline, imipramine, bromazepam, amitriptyline, and diazepam (**Table 1**). The notion that St. John's wort is efficacious in treating mild to moderate depression is further supported by a review of 6 further randomized clinical trials (17), which did not overlap with the previous meta-analysis (16). The methodologic quality was evaluated by using the Jadad score; 5 trials scored 5 points, and 1 scored 4 points.

Two further high-quality reviews applied stricter inclusion criteria (18, 33), and only 8 (18) and 6 (33) randomized, double-blind clinical trials were summarized (**Table 1**). All of these studies had been included in the two previous (16, 17) reviews. The methodologic quality of the primary studies was not formally assessed in either of the two later reviews. The authors confirmed that St. John's wort is more effective than placebo in the treatment of mild to moderate depression and is similar in effectiveness to low-dose tricyclic antidepressants.

The perhaps most critical meta-analysis (34) included 14 randomized clinical trials. All of these studies had been included in the two previous (16, 17) reviews. The authors did not formally assess trial quality. The results confirm that St. John's wort extracts were significantly more effective than placebo (relative benefit, 1.9 [CI, 1.2 to 2.8]) and equivalent to tricyclic antidepressants (relative benefit, 1.2 [CI, 1.0 to 1.4]). The authors found evidence of publication bias, which may have led to an overestimation of the effect.

A recent three-armed randomized clinical trial (35) that, in several respects, is the most rigorous trial on the subject to date was not included in the reviews discussed above. In this study, 263 patients with moderate depression received standardized St. John's wort extract, 1050 mg/d; imipramine, 100 mg/d; or placebo for 8 weeks. The results show that St. John's wort was more effective than placebo and equivalent to imipramine in reducing symptoms of depression, as verified by Hamilton Rating Scale for Depression scores.

In summary, St. John's wort appears to be efficacious in the treatment of mild to moderate depression.

Safety

Taken as monotherapy, St. John's wort has an excellent safety profile (**Table 3**) that is clearly superior to that of conventional antidepressants (36). The only potentially serious adverse effects are photosensitization, which is extremely rare, and induction of manic symptoms in predisposed patients (37). However, problems may arise when patients take St. John's wort with other medications. St. John's wort induces a hepatic enzyme through activation of the cytochrome P450 system (38). In addition, it probably activates P-glycoprotein, which further increases the elimination of synthetic drugs (39). Through these mechanisms, St. John's wort can decrease the plasma level of a large range of prescribed drugs (such as anticoagulants, oral contraceptives, and antiviral agents), with possible clinically serious consequences (19, 40, 41). Finally, some evidence indicates that the combination of St. John's wort with selective serotonin reuptake inhibitors can lead to serotonin overload or the serotonin syndrome, particularly in elderly patients (38).

Dosage

About 900 mg of standardized extract (usually standardized to 0.3% hypericin content) has been used in most trials. The clinical effect often takes 2 to 3 weeks to appear. Nonstandardized extracts may be grossly underdosed, and their use should be discouraged. In some European countries, St. John's wort is registered for the treatment of mild to moderate depression; in the United States, it is marketed as a dietary supplement.

Ginseng (*Panax ginseng*)

Complex terminology and lack of clear distinction between Siberian or Russian ginseng (*Eleutherococcus senticosus*) and Asian (Chinese or Korean) ginseng

Table 2. **Pharmacologic Profile of Top-Selling Herbal Medicinal Products**

Common Name	Latin Name	Main Active Constituents	Principal Pharmacologic Action
Ginkgo	*Ginkgo biloba*	Ginkgolides, bilobide, flavone glycosides	Multiple cardiovascular and other effects (such as antihypoxic, antiplatelet, and free radical scavenging) that may work together to protect tissue against ischemia
St. John's wort	*Hypericum perforatum L.*	Hypericin, hyperforin, and possibly others	Antidepressant (most likely through serotonin uptake inhibition), antiviral
Ginseng (Asian)	*Panax ginseng*	Ginsenosides, panaxans	Central nervous system stimulation (and suppression), hypertensive, antifatigue, hypoglycemic, antioxidant, anti-inflammatory, anticancer, platelet inhibition, immune stimulant, antineoplastic
Echinacea	*E. angustifolia*, E. pallida*, E. purpurea**	Polysaccharides, glycoproteins, alkamides, caffeic acid	Immune system stimulant, antifungal, anti-inflammatory
Saw palmetto	*Serenoa repens, Sabal serrulata*†	Fatty acids, sterols	Inhibits testosterone metabolism; anti-inflammatory
Kava	*Piper methysticum*	Kavalactones	Anxiolytic, muscle relaxant, mood enhancer, analgesic, sedative, antibacterial, platelet inhibitor

* Different species.
† Terms are synonymous.

Table 3. **Safety of Top-Selling Herbal Medicinal Products**

Common Name	Adverse Effects	Interactions	Contraindications*	Cautions†
Ginkgo	Gastrointestinal symptoms, headache, nausea, vomiting	May increase effects of anticoagulants	Concomitant anticoagulation, bleeding disorders	Warn patients to watch for bleeding and report such instances
St. John's wort	Very few when taken alone; nausea and allergic reactions are the most frequent	Probably acts as a hepatic enzyme inducer, thereby decreasing plasma levels of prescribed drugs Serotonin syndrome may result when herb is combined with selective serotonin reuptake inhibitors	Known photohypersensitivity	Do not give to children; watch for interactions with concomitant drug therapies; do not combine with prescription drugs
Ginseng (Asian)	Diarrhea, euphoria, headache, hypertension, hypotension, insomnia (relatively common), mastalgia, nausea, vaginal bleeding	May interact with monoamine oxidase inhibitors, stimulants, hypoglycemic agents, and warfarin	Cardiovascular disease, hypertension, hypotension, diabetes mellitus	"Ginseng abuse syndrome" has been described with prolonged use; do not take for prolonged time at high doses
Echinacea	Anaphylaxis (rare)	In theory, diminishes effects of immunosuppressants	Systemic progressive illness (such as HIV infection, collagen disease, multiple sclerosis, tuberculosis, and autoimmune diseases)	Rebound of immune system after discontinuation is conceivable; do not take for longer than 8 weeks; adulteration of products has been described
Saw palmetto	Constipation, decreased libido, diarrhea, headache, hypertension, nausea, urine retention	May in theory interact with hormonal medication	Women of childbearing age	May cause false-negative result on prostate-specific antigen test; exclude prostate cancer before starting herbal treatment
Kava	Reversible yellowish discoloring of skin, nails, and hair (chronic abuse); visual disturbances; dizziness; stupor; gastrointestinal discomfort; extrapyramidal effects (rare); hepatitis	Potentiates effects of other anxiolytics and alcohol	Children < age 12 y, renal disease, thrombocytopenia, neutropenia	Avoid concomitant use with psychotropic agents and long-term use

* None of these herbal medicinal products should be used in pregnancy or lactation or by people who are allergic to them.
† With all of these herbal medicinal products, instruct patients to report perceived adverse events promptly; data are insufficient on use of herbal medicinal products in infants and children.

(*Panax ginseng*) have generated confusion. The genus *Panax* includes other species, such as American ginseng (*P. quinquefolius*) and Japanese ginseng (*P. japonicus*). Unless stated otherwise, "ginseng" as discussed in this article pertains to *P. ginseng*.

Ginseng has been used for its alleged sedative, hypnotic, demulcent, aphrodisiac, antidepressant, and diuretic activity. It is often recommended to improve stamina, concentration, vigilance, and well-being (31). The pharmacologic activities of *P. ginseng* range from stimulation of the central nervous system to modulation of the immune system and anabolic effects (15). *Panax ginseng* has also been shown to accelerate hepatic lipogenesis and increase glycogen storage (42), which could contribute to an antidiabetic effect. The pharmacologic properties of Siberian ginseng are less well studied but are claimed to be similar to those of *P. ginseng* (15) (**Table 2**).

Efficacy

A systematic review of adequate quality included 16 randomized, double-blind, placebo-controlled clinical trials of any type of ginseng extract for diverse indications (43) (**Table 1**). Most of the primary studies were of low methodologic quality as judged by the Jadad score, but 6 studies had scores of 4 points. Many trials used healthy volunteers rather than patient samples. Evidence from sound clinical trials did not support the use of ginseng to treat the above-mentioned indications. In addition, a nonsystematic review of animal and human studies of ginseng as an ergogenic aid to physical performance (44) concluded that compelling evidence on the efficacy of ginseng for this indication is lacking.

A recent epidemiologic study (45) of a ginseng-growing region in Korea assessed the nutritional habits of 4634 inhabitants. During 5 years of follow-up, 137 cases of cancer were documented. Persons who regularly

consumed fresh Korean ginseng had a significantly reduced risk ratio for cancer of 0.31 (CI, 0.13 to 0.74). Moreover, a dose–response relation between risk for cancer and regular ginseng consumption was noted. Although this study cannot establish a causal relationship, its results seem to warrant further study.

Finally, a recent study showed that 3 g of American ginseng attenuated the postprandial glycemic response to a 25-g oral glucose challenge (46). The effect was seen in nondiabetic persons and in those with type 2 diabetes. The authors caution that American ginseng should be taken with a meal to prevent unintended hypoglycemia in nondiabetic persons.

Safety

Panax ginseng has several relatively serious adverse effects (8, 9, 31, 43), ranging from insomnia, diarrhea, vaginal bleeding, and mastalgia to severe headache, schizophrenia, and the Stevens–Johnson syndrome (**Table 3**). The exact incidence of these adverse effects is unknown but seems to be low. A probable interaction between warfarin and *P. ginseng* has also been observed (47). In that case report, a 47-year-old man whose anticoagulation had been controlled with warfarin experienced a subtherapeutic international normalized ratio of 1.5 after he self-medicated with ginseng at the recommended dose. The quality of many commercial ginseng products (sold as dietary supplements in the United States) is unknown, and adverse reactions might therefore be caused by contaminants.

Dosage

Formal dose-finding studies of ginseng have not been done. Usually, 0.5 to 2 g of dry ginseng root, equivalent to 200 to 600 mg of extract, is used as daily short-term treatment. For continuous administration, the equivalent of 1 g of dry root should not be exceeded. Low-quality products may be contaminated or contain no active ingredient at all; their use should be discouraged, and consumers should be advised to obtain products from reputable sources (**Table 1**).

Echinacea (*Echinacea* species)

Commercially available herbal medicines are produced from three species: *Echinacea angustifolia*, *E. pallida*, and *E. purpurea*. Different products use different parts of the plants, mostly roots. Thus, echinacea products vary considerably. Echinacea preparations contain many potentially active ingredients, such as polysaccharides, glycoproteins, alkamides, and flavonoids. No single active constituent has been found (20). Pharmacologic actions include stimulation of the immune system; local anesthesia; and anti-inflammatory, hormonal, antiviral, and free radical–scavenging activities (48) (**Table 2**).

Echinacea has traditionally been used topically and orally for diverse indications, including wound healing, abscesses, burns, eczema, and leg ulcers (9, 31). In vitro experiments suggest that a polysaccharide from *E. purpurea* increases the macrophage production of tumor necrosis factor-α, interleukin-1, and interleukin-B_2 (49). The best-researched indications are treatment and prevention of upper respiratory tract infections.

Efficacy

A Cochrane review (50) summarized 16 randomized clinical trials of echinacea for upper respiratory tract infection (**Table 1**). The methodologic quality of the primary studies, assessed by using the Jadad score, was found to vary; some studies were of good quality. Five trials of common cold prevention that had a placebo-control group tested five different echinacea preparations. Overall, the results were not conclusive. Three prevention trials with control groups that received no treatment suggested a beneficial effect. Of the 8 treatment trials (all placebo controlled), only 2 showed no significant effect in favor of the herbal medicinal products. The authors concluded that to date, evidence is insufficient to recommend a specific echinacea product. They also point out that publication bias may have distorted the results of their review. Thus, echinacea (particularly *E. purpurea*) may be efficacious, but the trial data are weak and inconclusive.

Safety

Adverse effects of echinacea preparations seem rare and consist mainly of allergic reactions, which can be severe (6, 8, 9, 31). The Australian Adverse Drug Reactions Advisory Committee received 11 reports of adverse reactions associated with echinacea between July 1996 and September 1997, including hepatitis (3 cases), asthma (3 cases), rash (1 case), rash with myalgia and nausea (1 case), dizziness with swollen tongue (1 case), and anaphylaxis (1 case) (51). Systematic studies of adverse effects of echinacea have not been done but are

needed, given the growing popularity of echinacea. A recent and probably underpowered study found no evidence of adverse pregnancy outcomes after echinacea consumption (21).

Dosage

Dose-finding studies are not available for echinacea. The usual recommended range is 900 to 1000 mg three times daily, equivalent to 6 to 9 mL of pressed juice or 0.75 to 1.5 mL of tincture daily. Some evidence indicates that preparations using juice of *Echinacea purpurea* are the best choice from the myriad commercial products on the market. The quality of the echinacea supplements on the U.S. market varies and is often unsatisfactory (52).

SAW PALMETTO (*SERENOA REPENS*)

The ripe berries of the American dwarf palm (*Serenoa repens* or *Sabal serrulata*) have been traditionally used to treat genitourinary problems; to enhance sperm production, breast size, or libido; and as a mild diuretic (9, 31). Today, saw palmetto is almost exclusively used to treat benign prostatic hyperplasia. The mechanisms of action are not fully understood. Animal experiments have demonstrated antiandrogen activity, and in vitro studies have shown inhibition of 5-α-reductase, the enzyme that converts testosterone to its active metabolite dihydrotestosterone (15). Another relevant pharmacologic action may be inhibition of estrogen receptors in the prostate (53). Reductions in size of the prostate gland have not been uniformly observed clinically.

Efficacy

A systematic review of good methodologic quality analyzed the data from 16 randomized, double-blind clinical trials involving 2939 patients with benign prostatic hyperplasia (54). The methodologic quality was estimated by using the scoring system of Schulz and was deemed to be good on average. Ten trials were placebo controlled and involved monopreparations, 3 used combinations of saw palmetto with other herbal medicinal products versus placebo, 2 compared saw palmetto with finasteride, and 1 compared it with another herbal medicinal product. The results show superiority of saw palmetto over placebo in terms of nocturia and peak urinary flow (**Table 1**) and suggest similar effectiveness compared with finasteride.

The existing trial evidence has been criticized; most of the studies are from Europe, and some have been judged to be of limited value, for instance, because only short-term treatment phases were used (22). A 6-month randomized, controlled trial from the United States recently confirmed that saw palmetto is "a safe and highly desirable option for men with moderately symptomatic benign prostatic hyperplasia" (55).

Thus, good evidence indicates that saw palmetto extract is efficacious short-term (and, probably, medium-term) therapy for symptoms of benign prostatic hyperplasia. In some European countries, saw palmetto is considered first-line therapy for this indication. However, data from large randomized clinical trials are not available.

Safety

Adverse effects of saw palmetto are rare and usually mild (**Table 3**). In all randomized clinical trials in the above-mentioned meta-analysis (54), withdrawal rates (a rough indicator of patient acceptance) were 9.1% for saw palmetto, 11.2% for finasteride, and 7.0% for placebo. No herb–drug interactions have been described.

Dosage

Dose-finding studies of saw palmetto are not available. The dose most often used in clinical trials is 320 mg of a liposterolic extract daily, equivalent to 20 g of crude berries. Treatment usually lasts 3 to 6 months, but no data from rigorous long-term studies are available.

KAVA (*PIPER METHYSTICUM*)

Kava is made from the dried rhizome of the kava plant. It is traditionally used in the South Pacific as a recreational drink. Kava has been used experimentally to attenuate seizures and to treat psychotic states (31). Today, it is mostly used for its anxiolytic effects.

The active ingredient is a family of four pyrones (kavapyrones). Their main pharmacologic properties are a central muscle-relaxing action and an anticonvulsant action (15). The mechanism of the anxiolytic effect is still somewhat controversial; one theory is that kavapyrones enhance γ-aminobutyric acid–binding in the amygdala without acting as direct antagonists at γ-aminobutyric acid receptors (56). Kavapyrones also are powerful strychnine antagonists (15) (**Table 2**).

Efficacy

A recent systematic review and meta-analysis of adequate quality (57) included seven randomized, double-blind, placebo-controlled clinical trials (**Table 1**). The

methodologic quality of the primary studies was assessed by using the Jadad score and was found to be variable but good on average; four of the studies scored the maximum of 5 points. Only three of the trials could undergo meta-analysis. The results demonstrated a reduction in Hamilton Rating Scale for Anxiety score in favor of kava, with a weighted mean difference of 9.7 points (CI, 3.5 to 15.8). One trial, not included in the above analysis, compared kava with oxazepam (58). Its results suggested that both medications are similarly efficacious anxiolytics. Collectively, these data suggest that short-term administration of kava is effective in reducing anxiety.

Safety

In randomized clinical trials, the incidence of adverse effects of kava was similar in the experimental and placebo groups (57). Serious adverse effects (**Table 3**) have been reported but seem to be rare. Two postmarketing surveillance studies involving more than 6000 patients found adverse effects in 2.3% and 1.5% of patients taking 120 to 240 mg of standardized extract (59, 60). Several cases of toxic liver damage were recently associated with kava self-medication (61). When kava is taken concomitantly with other medication that acts on the central nervous system or with alcohol, the effects of kava may be potentiated, leading to a temporal state of impaired vigilance or reduced consciousness; one such case has been reported (62).

Long-term use of kava at high doses is associated with flaky, dry, and yellowish discoloring of the skin; ataxia; hair loss; partial loss of hearing; loss of appetite; and body weight reduction. The dermatologic signs of excessive kava use are known as *kava dermopathy* or *kavaism* (63); they are usually reversible on discontinuation of use (64). Kavaism has thus far been observed only in inhabitants of the South Pacific, who regularly ingest doses at least 100 times higher than those recommended for therapeutic use (15).

Dosage

In randomized clinical trials, doses of kava have ranged from 70 to 240 mg of dried root extract, but the therapeutic window seems to be wide. Dosages up to 330 mg/d have been tested without increasing adverse effect rates (15).

Comment

It is encouraging that the current best-selling herbal medicinal products have been examined in randomized clinical trials and systematic reviews of those trials. Some herbal medicines discussed here are associated with seemingly positive risk–benefit profiles: ginkgo (for dementia and intermittent claudication), St. John's wort (as monotherapy for mild to moderate depression), and saw palmetto (for benign prostatic hyperplasia). For ginseng, echinacea, and kava, the evidence is less conclusive.

The discussions in this article are mostly based on systematic reviews. Their quality, as estimated according to published guidelines (23), is generally good or adequate. However, systematic reviews have limitations, particularly in the area of herbal medicine. They are often limited by the quality and quantity of the primary studies. Of note, high-quality systematic reviews may include weak primary studies, and strong primary studies do not guarantee that the quality of a review will be adequate. Moreover, systematic reviews usually assume that herbal medicinal products are comparable (which they are often not), and they are prone to publication bias. These problems can be minimized but can rarely be fully eliminated. Nevertheless, systematic reviews are more likely to arrive at correct conclusions than is any other method, except perhaps megatrials, which have not yet been done in herbal medicine.

Generally speaking, trials of herbal medicinal products have been too few, too small, and too short. The lack of long-term studies is especially unfortunate. Benign prostatic hyperplasia, for instance, clearly requires long-term therapy, but trials of saw palmetto to date are mostly short term (4 to 48 weeks) (22, 54). Thus, the clinician is caught between encouraging results of randomized clinical trials and the relative lack of controlled long-term data. The latter information is needed to make responsible therapeutic decisions.

It is often claimed that the herbal industry cannot sustain the high costs of long-term studies. Because herbal medicinal products cannot usually be patented, the incentives for research investments are much lower than in the pharmaceutical sector. These arguments, however, do not necessarily rule out research investments from the herbal industry. The figures for retail sales show that, in principle, money is not lacking; the challenge is to direct some of it to research. The industry might con-

Table 4. **Recent Publications on Herbal Medicine for a Professional Readership**

Publication	Strengths	Weaknesses
Blumenthal M, ed. The Complete German Commission E Monographs. Austin, TX: American Botanical Council; 1998.	Comprehensive; useful appendices	Not clinically oriented; not referenced; uncritical; not up to date
Blumenthal M, Goldberg A, Brinckmann J, eds. Herbal Medicine. Austin, TX: American Botanical Council; 2000.	Comprehensive; some clinical detail; well referenced	Based on Commission E monographs; in parts uncritical
Boon H, Smith M. The Botanical Pharmacy: The Pharmacology of 47 Common Herbs. Kingston, Ontario, Canada: Quarry Pr; 1999.	Most clinically oriented text available; detailed discussion; most important herbal remedies included; comprehensive references	Even more clinical orientation would be desirable; pocket format might be preferable
Brinker R. Herb Contraindications and Drug Interactions. Sandy, OR: Eclectic Medical Publications; 1998.	Comprehensive; well referenced; good reference text	Not entirely up to date; highly specialized
Cupp MJ. Toxicology and Clinical Pharmacology of Herbal Products. Totowa, NJ: Humana Pr; 2000.	Thorough on toxicology and pharmacology; well referenced	Includes only 28 herbal medicinal products, many of which are not in prevalent use; not clinically oriented
Ernst E, ed. The Desktop Guide to Complementary and Alternative Medicine: An Evidence-Based Approach. Edinburgh: Mosby; 2001.	Concise; clinically oriented; evidence-based; emphasis on safety; up to date; critical	Not comprehensive; low on detail; only key references included
Fetrow CW, Avila JR. Professional's Handbook of Complementary and Alternative Medicines. Springhouse, PA: Springhouse; 1999.	Comprehensive; critical; emphasis on pharmacology; good as a quick reference; useful key references	Not clinically oriented; not fully referenced
Focus on Alternative and Complementary Therapies. London: Pharmaceutical Pr; 2000. Available at www.ex.ac.uk/FACT/	Useful review journal; evidence-based approach; up to date	Not a reference text; deals with topics other than herbal medicine
Mazza G, Oomah BD. Herbs, Botanicals and Teas. Lancaster, UK: Technomic Publishing; 2000.	Thorough reviews; detailed pharmacology	Inconsistent chapters; not clinically oriented; not comprehensive
Newall CA, Anderson LA, Phillipson JD. Herbal Medicines. London: Pharmaceutical Pr; 1996.	Most important herbal remedies included; emphasis on pharmacology; good as a quick reference text; useful key references	Not clinically oriented; not comprehensive; not up to date
PDR for Herbal Medicines. Montvale, NJ: Medical Economics; 1998.	Comprehensive emphasis on pharmacology	Not clinically oriented; based on Commission E monographs; not up to date
WHO Monographs on Selected Medicinal Plants. vol. 1. Geneva: World Health Organization; 1999.	Detailed; emphasis on pharmacology; critical; comprehensive references	Not clinically oriented; not comprehensive; most popular herbal remedies not included in first volume

sider a system to create an association of reputable producers that sets aside a small percentage of each member's profits for the most urgent research projects (65). In the long run, the lack of reliable research data harms the herbal industry as well as the consumer.

The present lack of quality control and standardization of herbal medicinal products is of concern to many experts (66). Whenever such products are independently analyzed, the results show that an alarming proportion is contaminated (for example, by pesticides, herbicides, or heavy metals) or underdosed, or both (52). This situation is obviously unacceptable. It puts the consumer at risk and ultimately operates against the interests of the industry. Regulation of the herbal industry should address these problems by setting quality standards and subsequently branding them as noncompliant manufacturers. Meanwhile, consumers and health care professionals are at a loss when trying to decide which brands of herbal medicines to buy or recommend. One reasonable option is to use brands and extracts that have been tested in clinical trials (66) (**Table 1**).

Herbal medicine is plagued by several further problems. Many vocal and influential individuals insist that clinical research is not a priority. In their view, traditional knowledge and the "test of time" are adequate proof (67, 68). Yet the "test of time" is a notoriously poor guide for establishing the efficacy or safety of traditional therapies (69). The area of herbal medicine, it seems, has been hindered by a tradition of regarding clinical trials as being of secondary importance. However, such investigations, together with adequate postmarketing surveillance studies, are the best (and perhaps the only) way to answer the question of whether herbal medicinal products cause more good than harm.

Attitudes of the general public may be another problem. The present popularity of herbal medicinal products is largely due to the fact that the public perceives them as devoid of adverse effects (70). The media often help to perpetuate this myth (71). All herbal medicinal products are associated with finite risks; those covered in this review are probably safer than many others (6, 72). One issue that will gain relevance as research

progresses is the interactions between herbal medicines and prescription drugs (8, 9, 14, 19, 31, 32, 38–41, 72). The potential for such interactions is considerable (14), not least because all herbal medicines contain myriad ingredients (**Table 2**). It is possible, even likely, that at present we fail to recognize herb–drug interactions simply because we have no knowledge of them.

How should physicians inform themselves about herbal medicinal products? Books on the topic, written mostly for lay people, abound. According to our preliminary evaluation (73, 74), these books represent more of a risk to the health of the reader than a helpful source of knowledge. Fortunately, several recommendable publications for the professional readership have recently emerged (**Table 4**). Dissemination of objective rather than promotional information, stimulation of rigorous research, and provision of adequate funds (75, 76) are clearly the way ahead and should be in the interest of all parties concerned. Rigorous and systematic evaluation of all herbal medicinal products is urgently needed.

Requests for Single Reprints: Edzard Ernst, MD, PhD, FRCP(Edin), Department of Complementary Medicine, School of Sport and Health Sciences, University of Exeter, 25 Victoria Park Road, Exeter, Devon EX2 4NT, United Kingdom; e-mail, E.Ernst@exeter.ac.uk.

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