Review Article

Drug Therapy

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HERBAL REMEDIES

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HERBAL medicine is an increasingly common form of alternative therapy in the United States. A 1997 survey estimated that 12.1 percent of adults in the United States had used an herbal medicine in the previous 12 months (as compared with 2.5 percent in 1990), resulting in out-of-pocket payments of $5.1 billion.[1] Among those who had used herbal medicine, 15.1 percent had seen an alternative-medicine practitioner, with a total of 10.5 million office visits, 19.8 percent of which had been completely or partially covered by insurance.

REGULATION

Most herbal products in the United States are considered dietary supplements and thus are not regulated as medicines and are not required to meet the standards for drugs specified in the Federal Food, Drug, and Cosmetic Act. The only requirement is that these preparations meet the standards set forth in the 1994 Dietary Supplement and Health Education Act (DSHEA). Herbal products may be produced without the assurance of compliance standards for Good Manufacturing Practice (although such standards are being developed), and they are marketed without prior approval of their efficacy and safety by the Food and Drug Administration (FDA). According to the DSHEA, the manufacturer of an herbal preparation is responsible for the truthfulness of claims made on the label and must have evidence that the claims are supported, yet the DSHEA neither provides a standard for the evidence needed nor requires submission of the evidence to the FDA. Under the DSHEA, the manufacturer is permitted to claim that the product affects the structure or function of the body, as long as there is no claim of effectiveness for the prevention or treatment of a specific disease, and provided there is a disclaimer informing the user that the FDA has not evaluated the agent. Some of the claims on the labels of herbal products suggest that they can be used to treat disease, and accompanying materials, produced by persons other than the manufacturer, that overtly promote such use may be available where the herbal remedies are sold. According to the DSHEA, the manufacturer is responsible for controlling quality and safety, but if a concern about safety arises, the burden of proof lies not with the manufacturer but with the FDA, which has to prove that the product is unsafe.[2]

Several countries (e.g., Germany, France, Sweden, and Australia) have implemented strategies for licensing herbal remedies. In Germany, such products can be registered as medicines on the basis of information in approximately 300 monographs on herbs ("positive" monographs with concise information about terminology, composition, uses, contraindications, side effects, drug interactions, dosage, mode of administration, and actions, and "negative" monographs explaining insufficient benefits or unacceptable risks).[3] The European Commission (which governs the European Union) has recently promulgated a draft directive on the licensing of traditional herbal preparations. If accepted, this proposal will compel all members of the European Union to introduce a simplified procedure for these preparations so that they can receive a "traditional use" registration without the need to present data on efficacy from randomized trials.[4] The simplified licensing approach allows a premarketing assessment of the quality and safety of a product and facilitates post-marketing surveillance and product recalls[5]; it does not guarantee efficacy in the same stringent way that the approval process for conventional medications does.

QUALITY

If an herbal remedy is effective, quality assurance is needed to ensure that the product has the expected effects. Quality assurance is also important in the absence of data on efficacy, because quality is a critical determinant of safety as well. Herbal remedies should be controlled to make sure they do not contain adulterants or contaminants (Table 1). The quality of the available product information should also be ensured; the information should include basic data about the manufacturer, the composition and storage of the product, and its correct and safe use.[6]

Standardization of herbal remedies can be difficult,

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TABLE 1. POTENTIAL ADULTERANTS AND CONTAMINANTS THAT CAN AFFECT THE QUALITY OF HERBAL REMEDIES.*

TYPE OF ADULTERANT OR CONTAMINANT	EXAMPLES
Botanicals	Aristolochia, digitalis, colchicum, rauwolfia, plants containing belladonna or pyrrolizidine alkaloids†
Microorganisms	*Staphylococcus aureus, Escherichia coli* (certain strains), salmonella, shigella, *Pseudomonas aeruginosa*
Microbial toxins	Aflatoxins, bacterial endotoxins
Pesticides	Chlorinated pesticides, organic phosphates, carbamate insecticides and herbicides, dithiocarbamate fungicide, triazin herbicides
Fumigation agents	Ethylene oxide, methyl bromide, phosphine
Toxic metals	Lead, cadmium, mercury, arsenic
Drugs	Analgesic and antiinflammatory drugs (e.g., aminophenazone, phenylbutazone, indomethacin), corticosteroids, benzodiazepines; warfarin, fenfluramine, sildenafil[4]

*Data are from De Smet[6] and De Smet.[7]

†Replacement of *Stephania tetrandra* (fangji) with the root of *Aristolochia fangchi* (guangfangji) in a Belgian slimming cure that included conventional medicines resulted in numerous cases of progressive renal interstitial fibrosis, complicated in some persons by urothelial carcinoma characterized by DNA-adduct formation.[8] Similar problems may arise when the Chinese herbal ingredient mutong is taken from *A. manshuriensis* (guanmutong) instead of akebia or clematis.[9,10]

TABLE 2. POTENTIAL ADVERSE EFFECTS OF HERBAL REMEDIES AND THEIR MAJOR CONSTITUENTS.*

Cardiotoxicity
Aconite root tuber
Herbs rich in cardioactive glycosides
Herbs rich in colchicine
Leigongteng
Licorice root
Mahuang
Pokeweed leaf or root
Scotch broom†
Squirting cucumber†

Hepatotoxicity
Certain herbs rich in anthranoids
Certain herbs rich in protoberberine alkaloids
Chaparral leaf or stem
Germander species
Green-tea leaf†
Herbs rich in coumarin
Herbs rich in podophyllotoxin
Herbs rich in toxic pyrrolizidine alkaloids
Impila root
Kava rhizome
Kombucha
Mahuang
Pennyroyal oil
Skullcap
Soy phytoestrogens†

Neurotoxicity or convulsions
Aconite root tuber
Alocasia macrorrhiza root tuber†
Artemisia species rich in santonin
Essential oils rich in ascaridole
Essential oils rich in thujone
Ginkgo seed or leaf‡
Herbs rich in colchicine
Herbs rich in podophyllotoxin
Indian tobacco herb
Kava rhizome†
Mahuang
Nux vomica
Pennyroyal oil
Star fruit
Yellow jessamine rhizome

Renal toxicity
β-Aescin (saponin mixture from horse-chestnut seed)
Cape aloes†
Cat's claw†
Certain essential oils
Chaparral leaf or stem†
Chinese yew
Herbs rich in aristolochic acids
Impila root
Jering fruit
Pennyroyal oil
Squirting cucumber†
Star fruit

*The full version of this table is available from the National Auxiliary Publications Service (NAPS). (See NAPS document no. 05609 for 33 pages of supplementary material. To order, contact NAPS, c/o Microfiche Publications, 248 Hempstead Tpke., West Hempstead, NY 11552.) Adverse effects of multiple-herb therapies are not included. Case reports do not always provide adequate evidence that the remedy in question was labeled correctly. As a result, it is possible that some of the adverse events reported for a specific herb were actually due to a different, unidentified botanical or another adulterant or contaminant.

†A single case was reported without reference to previous cases.

‡Convulsions have been observed after large doses of yinguo (ginkgo seed), a traditional Asian food and medicine, which contains the convulsive agent 4′-*O*-methylpyridoxine (MPN).[12,13] Recently, anecdotal reports have associated ginkgo-containing preparations available on the Western market with seizures,[14] and these adverse events have also been reported in patients with seizure disorders stabilized by valproate.[15] How Western ginkgo preparations might induce seizures is still unclear. MPN has been detected in ginkgo leaf and preparations that contain it, but usually at subtoxic levels.[16]

because herbs contain complex mixtures and because the constituents responsible for the claimed effects are often unknown. Since herbal remedies are exempt from rigorous regulation in the United States, there may be considerable variation in the composition of an herbal remedy among manufacturers and lots, as well as discrepancies between label information and actual content.[11] For commonly used herbal remedies, the U.S. Pharmacopeial Convention is developing standards for product quality and monographs that review chemical, pharmacologic, and therapeutic data. When an herbal product is labeled "U.S. Pharmacopeia" or "National Formulary," the DSHEA requires that the product comply with the standards for product quality. Although this system may be useful to the extent that manufacturers are willing to abide by it, its voluntary nature leaves the door open for inferior products.

SAFETY

Contrary to popular belief, the use of herbal remedies can pose serious health risks. Besides the direct risks of adverse effects (Table 2) and drug interactions (Table 3), there is an indirect risk that an herbal remedy without demonstrated efficacy may compromise, delay, or replace an effective form of conventional treatment.[5]

Advocates of herbal remedies often present long-standing experience in traditional medicine as evidence of their safety, but this type of evidence has considerable limitations. It is easy to determine which botanicals contain substances that are so toxic that they have acute adverse effects in a large fraction of users. It is more difficult, however, to recognize adverse effects that develop over time (e.g., hypokalemia from anthranoid laxatives[3]), occur infrequently, or are readily ascribed to an underlying disease (e.g., hepatitis from the bile-duct remedy celandine[17]). If an herb caused an adverse reaction in 1 in 1000 users, a traditional healer would have to treat 4800 patients with that herb (i.e., 1 new patient every single working day

TABLE 3. POTENTIAL INTERACTIONS BETWEEN HERBS AND CONVENTIONAL DRUGS.*

HERB	CONVENTIONAL DRUG	COMMENTS
Ginkgo leaf	Acetylsalicylic acid Rofecoxib Warfarin	Ginkgo combined with acetylsalicylic acid,† rofecoxib,† or warfarin† has been associated with bleeding reactions; ginkgo alone has also been associated with bleeding (case reports).
	Trazodone	Coma was reported in a patient with Alzheimer's disease who took ginkgo leaf with trazodone.†
Hawthorn leaf or flower	Digitalis glycosides	Since hawthorn may exert digitalis-like inotropic effects, it is prudent to monitor persons taking this herb in addition to digitalis glycosides closely.
St. John's wort	5-Aminolevulinic acid Amitriptyline Cyclosporine Digoxin Indinavir Midazolam Nefazodone Nevirapine Oral contraceptives Paroxetine Phenprocoumon Sertraline Simvastatin Tacrolimus Theophylline Warfarin	A phototoxic reaction occurred in a patient simultaneously exposed to 5-aminolevulinic acid and St. John's wort†; in clinical studies, pretreatment with St. John's wort decreased the area under the curve for amitriptyline (and its active metabolite nortriptyline), digoxin, indinavir, midazolam, phenprocoumon, and the active metabolite of simvastatin (simvastatin hydroxy acid)‡; case reports have associated St. John's wort with reduced levels of cyclosporine (sometimes with transplant rejection), tacrolimus,† and theophylline†; with increased oral clearance of nevirapine; with intermenstrual bleeding or altered menstrual bleeding in users of oral contraceptives; and with reduced effects of phenprocoumon† and warfarin; lethargy and grogginess were reported in a patient taking St. John's wort and paroxetine,† and the serotonin syndrome has been reported in users of nefazodone† or sertraline (case reports); St. John's wort alone has also been associated with serotonin syndrome–like events (case reports).
Asian ginseng root	Phenelzine	Mania has been reported in a patient taking ginseng and phenelzine†; Asian ginseng alone has also been associated with mania.†
	Warfarin	A patient taking ginseng and warfarin had a decreased international normalized ratio.†
Garlic bulb	Ritonavir	Two brief case reports describe gastrointestinal toxic effects in patients taking garlic and ritonavir.
	Saquinavir	In a clinical study, the area under the curve for saquinavir decreased by 51 percent in patients taking garlic for 20 days; it returned to 65 percent of base line after a 10-day washout period.
	Warfarin	A brief case report described an increased clotting time in two patients taking warfarin and garlic; garlic alone has also been associated with bleeding (case reports).
Kava rhizome	Alprazolam Cimetidine Terazosin	Lethargy and disorientation were reported in a patient receiving this triple-drug regimen.†
Yohimbe bark	Centrally active antihypertensive agents	Yohimbine (a major alkaloid in yohimbe bark) may antagonize guanabenz and the methyldopa metabolite α-methylnorepinephrine through its α_2-adrenoceptor antagonistic properties.
	Tricyclic antidepressants	In clinical studies, tricyclic antidepressants increased the sensitivity to the autonomic and central adverse effects of yohimbine (major alkaloid in yohimbe bark).

*The full version of this table is available from the National Auxiliary Publications Service (NAPS). (See NAPS document no. 05609 for 33 pages of supplementary material. To order, contact NAPS, c/o Microfiche Publications, 248 Hempstead Tpke., West Hempstead, NY 11552.) Interactions associated with multiple-herb therapies are not included. Case reports do not always provide adequate evidence that the remedy in question was labeled correctly. As a result, it is possible that some of the interactions reported for a specific herb were actually due to a different, unidentified botanical or to another adulterant or contaminant.

†A single case was reported without reference to previous cases.

‡With the exception of phenprocoumon, these drugs are all substrates for cytochrome P-450 3A, P-glycoprotein, or both.

for more than 18 years) to have a 95 percent chance of observing the reaction in more than 1 user.[5]

Embryotoxic, fetotoxic, and carcinogenic effects of herbal remedies are also likely to remain unrecognized in traditional settings. Although aristolochia plants have been used for centuries, their capacity to induce urothelial carcinoma by DNA-adduct formation has only recently become clear.[8]

Another concern is that current Western use may not reflect the use of herbal preparations in traditional medicine. For example, an excellent safety record of a traditional oral preparation may well have limited meaning when the same herb is used in cigarettes. Moreover, herbs that are apparently safe under normal conditions may be more hazardous in specific patients, under special circumstances (e.g., during the perioperative period),[2] or when combined with conventional drugs (Table 3). In a recent U.S. survey, one in six adults taking prescription drugs reported concomitant use of at least one herbal or other product (not includ-

ing vitamin or mineral supplements) during the preceding week.[18]

EFFICACY

Only a small fraction of the thousands of medicinal plants used worldwide has been tested rigorously in randomized, controlled trials. The herbal industry is not required to conduct such trials, and many companies argue that it would be difficult to recover the high research costs, because herbal products can be patented less easily than newly synthesized drugs.[2] Yet randomized, controlled trials are the best way to demonstrate the efficacy of any medicine, herbal or conventional. However promising experiments in animals or anecdotal clinical experiences may seem and however widespread the use of a particular herb is, such observations cannot predict the results of appropriately designed randomized, controlled trials. This is illustrated by a recent trial in which adjuvant treatment with a mistletoe extract reputed to have anticancer properties did not affect disease-free survival or quality of life among patients with head and neck cancer.[19]

Positive findings from trials of various herbal preparations have been reported in recent years, but those results should not be accepted without considering the methods used and the quality of the data (Table 4). Systematic reviews and meta-analyses of such trials mostly show that the reported effects are rather limited, require confirmation by further well-designed studies with relevant clinical outcomes, or both (Table 5). Furthermore, data on direct comparisons of herbal remedies with well-established conventional medicines are too often unavailable or uninformative (e.g., the data are from studies that lacked a placebo group to assess the sensitivity of the study population to placebo[20]). To exemplify these points, four herbs — ginkgo, hawthorn, saw palmetto, and St. John's wort — that show promising evidence of efficacy and are widely used in the United States and Europe are discussed in detail below. Certain other popular herbal remedies for which promising evidence from randomized, controlled trials is not available (e.g., Asian ginseng[34,35] and echinacea[36,37,47]) or for which an unpredictable risk of serious toxicity apparently outweighs the reported benefit (e.g., kava, which has hepatotoxic effects that may sometimes necessitate liver transplantation[4,43,44]) are not considered.

STUDIES OF INDIVIDUAL HERBS

Ginkgo (*Ginkgo biloba*)

Ginkgo-leaf extracts are advocated primarily for the treatment of dementia (e.g., Alzheimer's disease), peripheral vascular diseases (e.g., intermittent claudication), and neurosensory problems (e.g., tinnitus).[3]

TABLE 4. CONCERNS ABOUT STUDY DESIGN AND DATA QUALITY IN RANDOMIZED, CONTROLLED TRIALS OF HERBAL REMEDIES.

The general methodologic quality is often rated as variable, owing to problems with, for example, randomization and blinding; for herbs that have a distinctive taste or smell, concealing the treatment assignment can be particularly problematic.
Besides scores for the general quality of trials, assessments should account for inclusion and exclusion criteria, the severity of the medical disorder studied, the number of patients enrolled, the adequacy of the run-in and treatment periods, and the use or nonuse of standardized symptom ratings and appropriate prespecified outcome measures.
Trial reports should specify the source, processing, and final composition of the herbal product; results obtained with one product may not apply to other preparations from the same herb; few trials have compared different preparations from the same plant source.
In the case of products that contain a mixture of herbal ingredients, the relative contribution of each may not be known.
Trial reports are often limited to the statistical significance of a mean difference between herb and placebo, whereas they could also present the number needed to treat for a minimal clinically important difference.
Intermediate outcomes (e.g., the effects of hawthorn on cardiac performance) instead of hard end points (e.g., effects on cardiovascular mortality) are often reported.
Most trials compare an herb with placebo but not with medications that have well-established safety and efficacy. When an herbal remedy is compared with an established synthesized compound, adequate doses of each are needed. The study should be adequately powered to detect clinically relevant differences in efficacy, and a placebo group is required if the study population is likely to have a substantial placebo response.[20]
Few trials have considered the combined use of an herbal medication and a conventional drug, but such use is common.
Positive results may be reported more often than negative results, leading to an overestimate of the treatment effect (publication bias); studies with positive results may have been overrepresented in journals of alternative medicine and may have been of poorer methodologic quality than corresponding studies with negative results.[21,22]

TABLE 5. SYSTEMATIC REVIEWS AND META-ANALYSES OF CONTROLLED TRIALS OF HERBAL PREPARATIONS.*

HERB	CONDITION	CONCLUSIONS AND COMMENTS
Ginkgo leaf	Dementia, intermittent claudication, tinnitus	For dementia, RCTs suggest superiority to placebo, with caveats[23]; for intermittent claudication, RCTs suggest superiority to placebo, but the effect size is limited and of uncertain clinical relevance[24,25]; for tinnitus, some trials report a benefit, but efficacy is unclear.[26]
Hawthorn leaf or flower	Heart failure	Placebo-controlled trials suggest improvements in cardiac performance and clinical symptoms in patients with mild heart failure.[27]
Saw palmetto fruit	Benign prostatic hyperplasia	RCTs suggest improvement in urinary symptoms and flow measures; long-term effectiveness and ability to prevent complications of benign prostatic hyperplasia are unknown.[28,29]
St. John's wort	Depressive disorders	RCTs suggest superiority to placebo for short-term treatment of depressive disorders that are mild to moderately severe.[30-33]
Asian ginseng root	Various indications	Efficacy is unclear for each indication[34]; additional randomized, controlled trials are needed.[35]
Echinacea	Prevention and treatment of common cold	Commercial products vary widely in composition; both positive and negative findings have been reported; additional properly designed trials with well-defined preparations are needed.[36,37]
Evening primrose oil	Premenstrual syndrome	The two best-controlled studies failed to show a benefit.[38]
Feverfew leaf	Prevention of migraine	The majority of RCTs favor feverfew over placebo, but with important caveats.[39]
Garlic bulb	Hypercholesterolemia	RCTs suggest possible small, short-term benefits on some lipid and antiplatelet factors; effects on blood pressure are mixed and small; methodologic problems in many trials; possibly variable release of allicin (a constituent of garlic) affected results; additional trials are needed.[40]
Ginger root	Nausea and vomiting	Promising data have been reported, but further rigorous trials are needed.[41]
Kava rhizome	Anxiety	RCTs suggest superiority to placebo, but caveats remain.[42]†
Silymarin (extract from milk-thistle fruit)	Liver diseases (e.g., cirrhosis)	RCTs with survival and other clinically relevant end points have had mixed results; further well-designed trials are needed.[45]
Valerian root	Insomnia	Data are inconclusive.[45]

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†Currently available evidence of efficacy is apparently outweighed by an unpredictable risk of serious hepatotoxic effects, which may sometimes necessitate liver transplantation.[4,43,44]

They contain terpenoids (ginkgolides and bilobalide) and flavonoids. Administration of ginkgo extracts has been associated with many in vivo central nervous system, cardiovascular, and neurosensory effects.[48] These effects have been attributed, in part, to platelet-activating factor antagonism of the ginkgolides[49] and the free-radical–scavenging and antioxidant properties of the flavonoids.[50] It is questionable, however, whether oral ginkgo preparations contain enough ginkgolides to cause platelet-activating factor antagonism in humans.[51]

Two long-term, randomized, placebo-controlled trials have shown positive effects of a well-defined extract (containing 6 percent ginkgolides and bilobalide and 24 percent flavonoids) in patients with Alzheimer's disease or multiinfarct dementia.[52,53] In the longer of these trials, subjects taking 40 mg of ginkgo extract three times daily had significant but limited improvement at 52 weeks, as compared with the placebo group, in mean scores for cognitive function (as measured by the cognitive subscale of the Alzheimer's Disease Assessment Scale) and daily behavior (as measured by the Geriatric Evaluation by Relative's Rating Instrument). However, the score on the Clinical Global Impression Scale did not differ significantly between the two groups.[53] After the first 26 weeks, 26 percent of the ginkgo-treated patients had at least a four-point improvement in cognitive function, and 23 percent had at least a four-point deterioration — changes that were significantly different from those in the placebo group (17 percent and 30 percent, respectively).[54] This result suggests that at least six patients would have to be treated to obtain a clinically meaningful change in one patient. Furthermore, although 79 percent of the patients were still in the trial after 26 weeks, only 44 percent completed it.[53] These positive results were

not corroborated by a recent trial, in which elderly persons with mild-to-moderate dementia or age-associated memory impairment took 80 to 120 mg of the same ginkgo extract or placebo twice daily.[55] However, age-associated memory impairment has been criticized as a broad and ambiguous concept.[56]

Meta-analyses show that randomized, placebo-controlled trials of ginkgo in patients with intermittent claudication have had mixed results, and only limited effects have been observed in the trials with positive findings.[24,25] In the largest randomized, controlled trial, the mean pain-free walking distance and the maximal walking distance increased by 45 m and 61 m, respectively, after 24 weeks of ginkgo treatment, as compared with increases of 21 m and 25 m, respectively, in the placebo group.[57] Although the differences were statistically significant, the effects were so small that they are of limited clinical relevance.[24,25,58] Only 7 of the 109 patients adhered to a walking program offered during the study, even though such a program can be of benefit in patients with intermittent claudication[24] and could have been tried before the ginkgo treatment was started.

A review of randomized, controlled trials of ginkgo in patients with tinnitus concluded that favorable results had been reported but that a firm conclusion about the efficacy of this treatment was not possible.[26] According to a recent report on a large, randomized, controlled trial, a regimen of 50 mg of ginkgo taken three times daily for 12 weeks was no more efficacious than placebo for the treatment of tinnitus.[59]

Ginkgo use has certain known problems. Oral ginkgo may occasionally cause headache, nausea, gastric symptoms, diarrhea, or allergic skin reactions.[3,60] Occasional anaphylaxis-like reactions have been reported with intravenous administration.[61,62] Case reports suggest that oral ginkgo may be associated with cerebral or extracerebral hemorrhage.[63-65] Bleeding has also been reported when ginkgo has been combined with aspirin, rofecoxib, or warfarin (Table 3). There are anecdotal reports that ginkgo preparations may be associated with seizures (Table 2) or the Stevens–Johnson syndrome,[66] and coma has been reported in a patient with Alzheimer's disease who took ginkgo and low-dose trazodone.[67]

Hawthorn (Crataegus Species)

Hawthorn extracts from the leaves and flowers of *Crataegus monogyna* and *C. oxyacantha* are advocated for mild heart failure (New York Heart Association class II).[3] Key constituents for their standardization are oligomeric procyanidins and flavonoids.[68] Among the reported effects in animal models are a positive inotropic action and prolongation of the effective refractory period,[69] some vasodilating properties,[70] and increased coronary blood flow.[70] Antiarrhythmic effects were reported in an ischemia–reperfusion model[71]; in a recent study, however, a hawthorn extract aggravated rather than prevented arrhythmias in such a model, and coronary blood flow remained unchanged.[72] Direct positive inotropic effects similar to the cyclic AMP–independent effects of digitalis glycosides have been observed in explants of left ventricular myocardium from patients with heart failure.[73] Moderate angiotensin-converting–enzyme inhibition has been reported in vitro,[74] but it is unclear whether this effect has any relevance in vivo.

According to a systematic review of randomized, placebo-controlled trials, hawthorn extracts may improve subjective symptoms and certain objective signs (e.g., exercise tolerance) in patients with mild heart failure (NYHA class II).[27] The trials that were reviewed were of variable methodologic quality,[75] and all were short (eight weeks or less). Most of the trials excluded patients with a more advanced stage of heart failure, and concomitant use of conventional cardiovascular drugs was not always well documented. A recent randomized trial compared a twice-daily regimen of 450 mg or 900 mg of a standardized hawthorn extract (containing 18.75 percent oligomeric procyanidins) with placebo as an adjuvant to diuretic treatment (hydrochlorothiazide and triamterene) in patients with stable NYHA class III heart failure.[76] After 16 weeks of therapy, the 1800-mg group had an increase in the maximal workload tolerated that was statistically significant as compared with the results in the placebo group, and both hawthorn doses caused a statistically significant reduction in subjective symptoms. Any treatment for symptomatic heart failure, especially with claims of inotropic activity, should be studied for a long period to determine potential adverse effects on survival, as has been the case with several synthetic inotropic drugs.[77] No such study of hawthorn has yet been reported. Whether hawthorn has an effect on mortality is currently under investigation in the Survival and Prognosis Investigation of Crataegus Extract trial, which is comparing a regimen of 450 mg of hawthorn extract taken twice daily with placebo as an adjuvant to conventional drug treatment in patients with congestive heart failure (NYHA class II or III and markedly impaired left ventricular function).[78]

Gastrointestinal symptoms, palpitations, chest pain, circulatory disturbances, and vertigo have been reported as occasional adverse effects of high-dose hawthorn extracts (900 to 1800 mg per day).[76,79,80] Vertigo or dizziness may not be a real adverse effect, because in a randomized, controlled trial, it occurred more often in the placebo group.[76] Since hawthorn has been reported to have positive inotropic effects that are similar to those of digitalis glycosides,[73] persons taking hawthorn in addition to digitalis glycosides should probably be monitored closely.[75]

Saw Palmetto (*Serenoa repens*)

Preparations of saw palmetto, or sabal fruit (*Serenoa repens,* or *Sabal serrulata*), have been advocated for the symptomatic treatment of mild-to-moderate benign prostatic hyperplasia. Clinically evaluated products contain a liposterolic extract standardized to contain 70 to 95 percent free fatty acids; these preparations also include phytosterols (such as β-sitosterol).[29] The mechanisms for the reported benefit of saw palmetto in patients with benign prostatic hyperplasia remain to be clarified. Reported in vitro effects include inhibition of 5α-reductase isoenzymes, inhibition of the binding of dihydrotestosterone to cytosolic androgen receptors in prostate cells, α_1-adrenoceptor antagonism, interference with prolactin-receptor signal transduction, and antiinflammatory activity.[29,81] In vivo studies have shown that saw palmetto decreases dihydrotestosterone levels and raises testosterone levels,[82] has antiestrogenic activity,[83] and increases apoptosis and reduces cell proliferation[84] in prostatic tissue from patients with benign prostatic hyperplasia. Unlike the 5α-reductase inhibitor finasteride, saw palmetto does not reduce the serum level of prostate-specific antigen and has little effect on prostate volume in men with benign prostatic hyperplasia.[85]

According to systematic reviews, standardized extracts of saw palmetto were superior to placebo in relieving symptoms of benign prostatic hyperplasia in several randomized, controlled trials, but the long-term effectiveness of such extracts, and their ability to prevent the progression and complications of benign prostatic hyperplasia, remain to be established.[28,29] Most of the studies that were reviewed were limited by small numbers of patients, a short duration of treatment (three months or less), failure to use standardized symptom scores, or a combination of these problems.[86] In a recent double-blind, randomized, controlled trial, the use of saw palmetto for six months significantly improved the International Prostate Symptom Score (on a scale from 0 to 35, with scores of 8 to 19 indicating moderate symptoms), as compared with placebo (a difference in the change from the base-line score of 2.2 points).[86] Changes in the peak urinary flow rate, quality of life, and sexual function did not differ significantly between the treatment and placebo groups.[86] The absence of an effect on the flow rate may have been related to the inclusion of patients with normal flow rates. In large randomized, controlled trials, saw palmetto provided symptomatic relief similar to that of finasteride[85] or the α_1-adrenergic antagonist tamsulosin.[87] However, these trials lacked placebo groups to assess the sensitivity of the study population to placebo.[85,87]

In placebo-controlled trials, the adverse effects of saw palmetto (e.g., gastrointestinal symptoms) have generally been mild and similar to those of placebo.[28,86] In the trials comparing saw palmetto with finasteride or tamsulosin, saw palmetto was associated with various symptoms (e.g., rhinitis and headache) as intercurrent events. The incidence of these events did not differ significantly from the incidence in the other treatment groups, with one exception: ejaculation disorders occurred significantly more frequently in patients taking tamsulosin (4.2 percent) than in those taking saw palmetto (0.6 percent).[85,87] One case of intraoperative hemorrhage has been associated with saw palmetto.[88]

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

St. John's wort is promoted for depression, anxiety, and nervous unrest.[3] The herb contains naphthodianthrones (hypericin and pseudohypericin), phloroglucinols (hyperforin and adhyperforin), phenylpropanes, flavonol derivatives, biflavones, proanthocyanidins, xanthones, and amino acids.[89] The question of which constituents lead to the reported clinical effects is still under investigation.[90] In the past, extracts were most often standardized for hypericins, but remarkably, no measurable amounts of hypericin cross the blood–brain barrier after intravenous administration of massive doses in nonhuman primates.[91] In recent years, the focus has shifted to hyperforin as a major constituent. Hyperforin inhibits the synaptic uptake of serotonin, dopamine, norepinephrine, γ-aminobutyric acid, and L-glutamate in vitro,[92] but in vivo experiments in animals suggest that St. John's wort does not act like a conventional selective serotonin-reuptake inhibitor[91] and that the spectrum of its central nervous system activity does not fully depend on the hyperforin content.[93] According to other studies in animals[94] and anecdotal clinical evidence,[95] St. John's wort may have anxiolytic activity. However, data from randomized trials of St. John's wort in patients with primary anxiety disorders are not yet available.

Systematic reviews suggest that St. John's wort is more efficacious than placebo for the short-term treatment of depression that is mild or moderate.[30-33] Concern has been expressed about the methodologic quality of the randomized, controlled trials and about potential publication bias.[31,96,97] One review stated that rates of response to St. John's wort were 23 to 55 percent higher than rates of response to placebo but identified only one of the randomized, controlled trials as a study without methodologic flaws.[30] Even that trial has raised some questions.[97] On the basis of a similar meta-analysis,[31] a guideline of the American College of Physicians–American Society of Internal Medicine states that St. John's wort may be considered for short-term treatment of mild acute depression, provided that patients are cautioned that this treatment is not approved by the FDA and that preparations may vary substantially from those tested in randomized trials.[98]

The positive tone of systematic reviews of the efficacy of St. John's wort in patients with depression that is moderate is not corroborated by two new rigorous randomized, controlled trials, in which an eight-week regimen of St. John's wort was compared with placebo in outpatients with major depression (as defined by the *Diagnostic and Statistical Manual of Mental Disorders,* fourth edition) of at least moderate severity (a score of 20 or higher on the 17-item Hamilton Rating Scale for Depression).[97,99] In the first trial, which evaluated a regimen of 300 mg of extract (standardized for hypericin) taken three to four times daily, the rates of change in scores on the Hamilton Rating Scale for Depression and the Hamilton Rating Scale for Anxiety did not differ significantly from those with placebo, nor was there a significant difference in response rates (26.5 percent for St. John's wort and 18.6 percent for placebo). The remission rate with St. John's wort was significantly higher than that with placebo, but both rates were very low (14.3 percent and 4.9 percent, respectively).[97] The mean duration of the episode of depression was 2.5 years, which may have minimized the rate of spontaneous recovery but which may also limit the generalizability of the findings. The study did not include a third group to assess the response to an adequate dose of a conventional antidepressant.[20] The importance of such an additional group is evident from the second trial, in which neither an extract of St. John's wort standardized to contain 0.12 to 0.28 percent hypericin (300 to 500 mg taken three times daily) nor the active comparative drug, sertraline (50 to 100 mg per day), differed significantly from placebo with respect to changes in the score on the Hamilton Rating Scale for Depression or the full-response rate (the primary outcome measures). Unlike St. John's wort, sertraline was more effective than placebo with respect to the score on the Clinical Global Impression of Improvement Scale (a secondary measure) at week 8.[99]

The only other three-group, randomized, controlled trial that has been reported compared an extract of St. John's wort containing 2 to 3 percent hyperforin and 0.2 to 0.3 percent hypericins (350 mg three times daily) with placebo and with imipramine (100 mg daily) for eight weeks in patients with moderate depression (as defined by the *International Classification of Diseases, 10th Revision*) and scores of 18 or more on the Hamilton Rating Scale for Depression.[100] St. John's wort was significantly more efficacious than placebo and as efficacious as imipramine in reducing the mean score on the Hamilton Rating Scale for Depression (the primary efficacy measure). With respect to the response rate (a secondary measure), St. John's wort was also significantly better than placebo (with a response rate of 76 percent vs. 63 percent) and similar to imipramine (67 percent), which did not differ significantly from placebo. In other words, about eight patients would have to be treated with St. John's wort to obtain one more response than with placebo. The high rate of response to placebo raises a question about the generalizability of these findings to other populations with depression. Other randomized, controlled trials comparing St. John's wort directly with a tricyclic antidepressant[101-103] or a selective serotonin-reuptake inhibitor[104-108] all lacked a placebo group to assess the sensitivity of the study population to placebo. These trials have also had other methodologic problems,[30,97] such as insufficient power in several studies,[33] and most excluded severely depressed patients. On the basis of the current evidence, St. John's wort should not be substituted for a conventional antidepressant in patients with moderately severe or severe major depression.

In short-term trials, St. John's wort has been well tolerated. In comparative studies, it was associated with adverse events and withdrawals related to adverse events less often than were tricyclic antidepressants, and this finding is claimed to be beneficial with respect to compliance.[100-103] However, the difference in withdrawal rates related to adverse events was much less marked in the trials comparing St. John's wort with selective serotonin-reuptake inhibitors (4.0 percent and 6.3 percent, respectively)[99,104-108] than in the trials comparing St. John's wort with tricyclic antidepressants (2.4 percent and 10.4 percent, respectively).[100-103]

Adverse events reported during the use of St. John's wort include gastrointestinal symptoms, dizziness or confusion, fatigue, dry mouth, restlessness, headache, allergic skin reactions, sexual dysfunction, frequent urination, and swelling.[99,109] Large amounts of St. John's wort can cause phototoxic effects in grazing animals. Although the responsible hypericins did not reach phototoxic levels when therapeutic doses were given to healthy volunteers,[110] there are reports of photosensitivity reactions in users of St. John's wort (e.g., in patients undergoing ultraviolet or laser treatment).[111-113] Mania,[108,114] psychotic relapse in patients with schizophrenia,[115] serotonin syndrome–like events (e.g., anxiety, confusion, hypertension, and diaphoresis),[116,117] hypertensive crisis,[118] cardiovascular collapse during the administration of anesthesia,[119] delayed emergence from general anesthesia,[120] and elevated thyrotropin levels[121] have also been reported as possible adverse effects.

Reported interactions between St. John's wort and conventional drugs are summarized in Table 3. The combination of St. John's wort and serotonin-reuptake inhibitors has been associated with a central serotonin syndrome. St. John's wort can also reduce the plasma levels or efficacy of various conventional medicines. Although the latter effect has not been reported in clinical studies in which the herb was used for 8 days or

less, treatment for 14 or more days can lead to marked changes.[122] Induction of cytochrome P-450 3A and P-glycoprotein has been suggested as the underlying mechanism.[123-125] St. John's wort and hyperforin both activate the steroid X receptor in vitro, which induces hepatic cytochrome P-450 3A activity in response to endogenous steroids and exogenous drugs.[126] Hypericin does not have this effect,[126] but contributes to P-glycoprotein induction by St. John's wort in vitro.[127]

RECOMMENDATIONS

Clinicians should not prescribe or recommend herbal remedies without well-established efficacy as if they were medications that had been proved effective by rigorous study. However, these products continue to have great appeal to patients, and this reality cannot be ignored. Thus, it is imperative to ask patients whether they are taking herbal products, particularly when they present with an unexplained health problem. Clinicians must be informed about the potential effects of herbal preparations and must be able to discuss this subject in a nonjudgmental way. They must tread a line between an apparently sympathetic stance that might be interpreted as an endorsement of unproven therapies and categorical disapproval, which would discourage patients from revealing their use of herbal remedies. There is no straightforward formula for achieving a balanced approach; the discussion should be tailored to the individual patient in an effort to convey professional views that the patient will both understand and respect. The physician will then have an opportunity to outline the available clinical data on the efficacy of herbal products and to explain which potential hazards should not be overlooked.

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