Herbal medicines are widely used in the United States, with approximately one quarter of adults reporting use of an herb to treat a medical illness within the past year. Herbs contain complicated mixtures of organic chemicals, the levels of which may vary substantially depending upon many factors related to the growth, production, and processing of the herbal product. While many manufacturers attempt to provide products with consistent levels of suspected active ingredients through a process known as standardization, this technique has uncertain effects on the safety and efficacy of the final product. Herbs are considered to be dietary supplements in the United States and therefore are subjected to a very limited form of regulation and oversight. Although herbs are often believed to be “natural” and therefore safe, many dangerous and lethal side effects have recently been reported, including direct toxic effects, allergic reactions, effects from contaminants, and interactions with drugs and other herbs. Of the ten most commonly used herbs in the United States, systematic reviews have concluded that only four are likely to be effective, and there is very limited evidence to evaluate the efficacy of the approximately 20,000 other available herbal products. Because herbs may contain potent bioactive substances and are often marketed to treat specific diseases, many have argued that they should be subject to more stringent regulation, similar to over-the-counter drugs. To improve the safety and consistency of herbs, additional research is needed to define the pharmacology, stability, and bioavailability of these products.


PREVALENCE/EPIDEMIOLOGY

Numerous surveys have shown that a large percentage of the population in the United States uses herbs to treat medical illness or improve health. In the most widely publicized national survey of complementary and alternative medicine use, Eisenberg et al found that the percentage of adults using herbs to treat medical conditions rose from 3% in 1990 to 12% in 1997 (1). A separate national telephone survey of 1500 adults conducted in 1997 found that 17% of adults reported use of herbal products within the past year (2). A population-based survey in Michigan found that 21% of adults reported using herbs in 2001 (3). Other recent surveys in Minnesota and Mississippi have found even higher estimates of use (61% to 71%) (4,5). Herbal products are also commonly used by patients with certain chronic medical conditions, including breast cancer (12%) (6), liver disease (21%) (7), human immunodeficiency virus (22%) (8), asthma (24%) (9), and rheumatological disorders (26%) (10). Herbal product annual retail sales have reflected the growing consumer interest, increasing approximately 25% per year from $1 billion in 1994 to $4 billion in 1998 (11). Although the estimated percentage of adults currently using herbs varies and depends upon differences in survey methodology, it is clear that herbs are used by a large and growing percentage of the population.

THE COMPLEXITY OF HERBAL PRODUCTS

Herbs are generally defined as any form of a plant or plant product, including leaves, stems, flowers, roots, and seeds (12). Herbal products may contain a single herb or combinations of several different herbs believed to have complementary effects. Some herbal products, including many traditional Chinese medicine formulations, also include animal products and minerals (13).

Herbal products are sold as either raw plants or extracts of portions of the plant. Extraction involves boiling or percolating the herb in water, alcohol, or other solvents to release biologically active constituents of the plant. These liquid extracts may then be heated or dried to create more concentrated liquids, pastes, or powders.

Both the raw herb and the extract contain complicated mixtures of organic chemicals, which may include fatty acids, sterols, alkaloids, flavonoids, glycosides, saponins, tannins, and terpenes (13). It is often difficult to deter-
mine which component, if any, of the herb has biological activity in humans. In addition, the processing of herbs, such as heating or boiling, may alter the pharmacological activity of the organic constituents. Similarly, a host of environmental factors, including soil, altitude, seasonal variation in temperature, atmospheric humidity, length of daylight, rainfall pattern, shade, dew, and frost conditions, may affect the levels of components in any given batch of an herb. Other factors, including infections, insects, planting density, competition with other plant species, seeding time, and genetic factors, play an important role in producing uniform herbal products (14).

Because of the multiple factors that affect the concentration of active ingredients in the final herbal product, some manufacturers have attempted to create a more consistent product through standardization, which involves identifying certain unique chemical components of the herbs known as markers and altering the production process to achieve a consistent level of these markers in every final batch of the herbal product. Currently, some herbal markers are known to have pharmacological activity, but very few are known to have clinical effects.

One common standardization process involves blending several batches of the same herb that contains different amounts of the desired marker. This blending process may produce an extract with the desired amount of the standardized component, but the effect on the other “nonstandardized” ingredients is not clear. Some manufacturers have tried to address the standardization problem by adding purified active markers to an extraction (e.g., by adding just the active marker, hyperforin, to a batch of St. John’s wort). This approach will produce a uniform amount of the standardized component in the final extract, but the final product will not contain the original balance of organic ingredients found in the extract. Standardization therefore may have unpredictable effects on the toxicity profile of an herbal extract and becomes far more complex when multiple herbs are involved in a single product.

**Regulations**

In the United States, herbs are considered dietary supplements and are subject to regulation as specified in the Dietary Supplement Health and Education Act of 1994 (15), which provides a very different framework for the regulation of herbal products than for pharmaceutical drugs in terms of establishing efficacy, safety, and post-marketing surveillance. This congressional action arose in response to the prevailing belief that herbs were safe, and that the public desired increased access to herbs and other dietary supplements that would be largely unavailable if subjected to the same restrictions as pharmaceutical drugs (16).

Herbs and other dietary supplements may not claim to “treat, prevent, cure, mitigate, or diagnose a specific disease;” these claims are limited to drugs, and drug manufacturers must submit proof of safety and efficacy and receive approval from the Food and Drug Administration (FDA) before sale and marketing. The drug approval process is expensive and time consuming, and one of the goals of the Dietary Supplement Health and Education Act was to allow for the production and sale of herbs and dietary supplements that might have some pharmacological effect, but that did not have the extensive evidence required to support a health claim. Under this Act, dietary supplement manufacturers may make certain claims, including “structure/function claims,” without proof of safety and efficacy. These claims “describe the role of the nutrient or dietary ingredient intended to affect the structure of function of the body” (15). Examples of these claims include wording such as “improves optimal prostate health,” or “maintains a healthy immune system.” However, a recent study of health claims made by herbal product manufacturers on the Internet found that 55% illegally claimed to treat, prevent, diagnose, or cure specific diseases (17). Others have suggested that the FDA does not have the resources to adequately monitor dietary supplement manufacturers and their advertising claims, and that the current regulatory system is not effective in protecting consumers from the risks associated with certain herbal products (18).

Herbal product manufacturers are not required to submit evidence of safety to the FDA, and this agency does not “approve” or analyze herbal products before they are sold and marketed. Although the Dietary Supplement Health and Education Act states that the manufacturer is responsible for ensuring the safety of herbal products (15), there are no FDA regulations that specify how safety should be established. With herbs and all other dietary supplements, the FDA bears the legal burden of proving that a product is unsafe before it can be removed from the market. The law does not require manufacturers to report adverse events to the FDA (19).

Several studies have shown that existing herbal products vary widely in the amounts of active markers in the product. For example, a recent analysis of 25 available ginseng products found a 15- to 200-fold variation in the concentration of the two ingredients believed to have biological activity; ginsenosides and eleutherosides (20).

The very limited oversight of herbal products in this country contrasts sharply with regulations in many other countries. In most European countries, premarket approval is required for herbal medicinal products. Germany, France, Sweden, Denmark, and Switzerland have established specific national regulations concerning the evaluation of herbal products. In addition, the European Union has issued multiple directives on manufacturing, quality-testing, and evaluating herbal products. Other countries like The Netherlands, Portugal, Japan, and China regulate them as pharmaceuticals and manufac-
turers in these countries must comply with Good Manufacturing Practice requirements and, increasingly, Good Agriculture Practice requirements (21).

Efficacy
Herbs have been used for centuries to treat illness and improve health, and still account for approximately 80% of medical treatments in the developing world (22). However, there is very limited evidence from randomized controlled trials to support the efficacy of the vast majority of herbal products. Of the ten most commonly used herbs in the United States in 2001 (Table 1), systematic reviews have found statistically significant evidence of efficacy for only four herbs: garlic, *Ginkgo biloba*, saw palmetto, and St. John’s wort.

In the most recent systematic review of garlic for hypercholesterolemia (23), garlic was estimated to decrease total cholesterol levels by 4% to 6% greater than placebo. This systematic review included five new studies, excluded studies of lower methodological quality, and found a smaller effect than the 9% to 12% reduction in total cholesterol levels reported in two earlier systematic reviews (24,25). The 4% to 6% reduction in total cholesterol levels is similar to that found with dietary intervention (26) and much smaller than the 17% to 32% reduction found with the use of statin drugs (27,28). The active ingredient in garlic is believed to be the sulfur-containing compound, allicin, which inhibits cholesterol synthesis by deactivating 3-hydroxy-3-methylglutaryl coenzyme A reductase (29).

Two systematic reviews evaluating the use of *G. biloba* to treat dementia concluded that the herb is significantly more effective than placebo in delaying cognitive deterioration (30,31). A third systematic review found promising evidence of efficacy, but also noted methodological problems in the included studies and suggested the need for new, larger trials (32). By pooling the results of prior studies, one systematic review concluded that the use of *G. biloba* led to a 3% improvement in the Alzheimer’s Disease Assessment Scale-Cognitive subtest (30), an improvement comparable to that seen with the pharmaceutical drug, tacrine (33). A recent high-quality randomized controlled trial found that *G. biloba* was not effective for improving cognitive function in elderly adults without dementia (34). The active ingredients in *G. biloba* extract are believed to be flavonoids and terpenoids. The flavonoids have antioxidant properties and are able to improve cerebral and peripheral blood flow through nitric oxide–induced vasodilation. The terpenoids inhibit binding of platelet-activating factor, which is normally a potent mediator of inflammation (13).

Although prior studies of saw palmetto are limited in terms of duration and outcome measurements, a recent systematic review concluded that the herb improves urinary tract symptoms and flow rates (35). In two separate studies, saw palmetto was found to have efficacy similar to finasteride (36,37). Three small studies were conducted after the systematic review (38–40), and only one (38) found a statistically significant benefit in urinary symptoms. A much larger study is ongoing and is targeted for completion in 2004 (41). Saw palmetto extracts contain primarily free fatty acids with a smaller component of sterols, including beta-sitosterol. The mechanism of action of this extract is not known, but anti-inflammatory activity, antiandrogen effects, 5-alpha-reductase inhibition, and growth factor inhibition have been proposed (13).

St. John’s wort has been evaluated in five systematic reviews, all of which concluded that the herb is beneficial in the treatment of depression (42–46). A comparison between St. John’s wort and the tricyclic antidepressant, imipramine, found the herb to be more effective with fewer side effects (47). Two recent randomized controlled trials conducted in the United States found that the herb was not effective in major depression (48,49), suggesting that it may only be effective for mild to moderate forms of the disease or that prior studies were methodologically flawed. Studies suggest that the active ingredients in St. John’s wort are hypericin and hyperforin, which inhibit the reuptake of monoamines, including serotonin, noradrenaline, and dopamine, as well as the amino acid neurotransmitters γ-aminobutyric acid and glutamate (50).

The evidence for efficacy of the remaining six of the 10 most commonly used herbs is extremely limited. A systematic review of echinacea found eight studies that examined efficacy for treatment of the common cold (51). Although six studies reported positive results, the variations in study design and outcome assessment made it difficult to definitively determine efficacy. Two recent randomized placebo-controlled trial of echinacea, one for treatment of the common cold in 148 college students in the United States (52), and another for prevention of the common cold in 109 adult clinic patients in Germany (53), found no benefit. Systematic reviews of ginseng (54) and aloe (55) did not find evidence to conclude that these herbs were effective for the treatment of any condition. Similarly, there is very limited evidence to evaluate the efficacy of the remaining three herbs—grape seed extract, green tea, and bilberry—and systematic reviews for these products have not been published.

Although herbs used to treat menopausal symptoms were not among the 10 most commonly used herbs, they are likely to gain popularity now that the benefits of hormone replacement therapy have come into question (56). A recent systematic review of herbal therapies for menopausal symptoms concluded that only one herb, black cohosh, may be effective for hot flashes, based on the identification of four randomized controlled trials, three of which found a benefit (57). However, no clinical trials have lasted more than 6 months, and the authors were
## Table 1. Efficacy of the Ten Most Commonly Used Herbs

<table>
<thead>
<tr>
<th>Herb</th>
<th>Herbal Sales in 2001 (%)(^a)</th>
<th>Common Use(^\dagger)</th>
<th>Systematic Review(s) of Evidence</th>
<th>Conclusions Regarding Efficacy(^\ddagger)</th>
<th>Comments (Reference)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Echinacea</td>
<td>6.5</td>
<td>Upper respiratory tract infection</td>
<td>Yes (51)</td>
<td>Variations in quality and design of included studies prevented a formal meta-analysis. Six of eight studies reported a positive result.</td>
<td>Two subsequent studies, one for treatment, (52) and one for prevention (53), found no benefit</td>
</tr>
<tr>
<td>2. Garlic</td>
<td>6.1</td>
<td>Hyper-cholesterolemia</td>
<td>Yes (23)</td>
<td>Total cholesterol reduced by 4% to 6% (equivalent to a decreased plasma concentration of (-0.41) mmol/L, 95% CI, (-0.66) to (-0.15))</td>
<td>Inclusion of five new studies and exclusion of lower quality studies resulted in a smaller benefit than the 9% to 12% reduction reported in earlier systematic reviews (24,25)</td>
</tr>
<tr>
<td>3. <em>Ginkgo biloba</em></td>
<td>4.2</td>
<td>Dementia, cognitive impairment</td>
<td>Yes (30–32)</td>
<td>Alzheimer’s Disease Assessment Scale cognitive subtest improved approximately 3%</td>
<td>Methodological problems in included studies suggest the need for new, larger studies</td>
</tr>
<tr>
<td>4. Saw palmetto</td>
<td>4.2</td>
<td>Benign prostatic hyperplasia</td>
<td>Yes (35)</td>
<td>Relative risk for improvement in self-rating of urinary tract symptoms was 1.72 (95% CI, 1.21 to 2.44)</td>
<td>Of three small studies not included in this systematic review (38–40), only one (38) found a benefit. A large study is ongoing (41)</td>
</tr>
<tr>
<td>5. Ginseng</td>
<td>3.4</td>
<td>Physical performance</td>
<td>Yes (54)</td>
<td>Not effective</td>
<td>Of the seven included studies, the four most recent found no improvement</td>
</tr>
<tr>
<td>6. Grape seed extract</td>
<td>3.2</td>
<td>Venous insufficiency</td>
<td>No N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>7. Green tea</td>
<td>3.1</td>
<td>Cancer</td>
<td>No N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>8. St. John’s wort</td>
<td>3.0</td>
<td>Depression</td>
<td>Yes (42–46)</td>
<td>56% of St. John’s wort patients responded vs. 25% of placebo patients</td>
<td>Two recent trials found no benefit in patients with major depression, (48,49) suggesting that the herb may only be effective for mild-moderate symptoms</td>
</tr>
<tr>
<td>9. Bilberry</td>
<td>3.0</td>
<td>Vision impairment</td>
<td>No N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>10. Aloe</td>
<td>2.9</td>
<td>Dermatitis/Wound healing (topical)</td>
<td>Yes (55)</td>
<td>Limited evidence</td>
<td>Two studies in patients with radiation induced dermatitis found no effect; one trial found faster wound healing, while a second found delayed wound healing</td>
</tr>
</tbody>
</table>

\(a\) Percent of herbal product sales for herbs were reported in a published survey of retail natural product stores (77).

\(\dagger\) Descriptions of common use are based on opinions cited in two commonly used textbooks of herbal medicine (13,78).

\(\ddagger\) Conclusions regarding efficacy are based on findings of the cited systematic reviews and randomized controlled trials published later.

Systematic reviews were identified by searching MEDLINE with a title word search for each herb name, and by searching the Cochrane Collaboration Database of Systematic Reviews through August, 2003. Randomized controlled trials published after the identified systematic reviews were also identified with a title word search for the herb name in MEDLINE through August, 2003. Reference lists of all retrieved articles were also scanned for relevant studies. CI = confidence interval, N/A = not applicable.
concerned that long-term use of black cohosh might cause endometrial or breast stimulation (57). The active ingredients and the mechanism of action of black cohosh are not known.

Despite the limited evidence for these 10 commonly used herbs, there is likely far less or no evidence for the remainder of the estimated 20,000 herbal products (12) available in the United States. The situation is no better for Chinese herbs; a recent review of Chinese herbs used for respiratory tract illness found that evidence to support efficacy was extremely limited (58). A more extensive review of randomized controlled trials published in traditional Chinese medicine journals found many methodological flaws in the vast majority of studies, including inadequate blinding, improper controls, no information on withdrawals or dropouts, and improper statistical analyses (59). Another review of studies examining the efficacy of complementary and alternative medical therapies concluded that most randomized controlled trials in this field are of poor quality (60).

Safety
Herbal products are often perceived as safe because they are “natural” (22). However, herbs contain potent bioactive substances; nearly one third of pharmaceutical drugs were originally derived from plants (12). Many dangerous and lethal side effects have been reported from the use of herbal products (61). These side effects may occur through several different mechanisms, including direct toxic effects of the herb, allergic reactions, effects of contaminants, and interactions with drugs or other herbs.

Recent publications have highlighted the severe consequences from side effects from certain herbal products, which often affect otherwise healthy patients seeking solutions to problems such as obesity. A recent case series described a group of 104 women who developed Chinese herb nephropathy after taking herbal weight-loss products containing the herb *Aristolochia fangchi* (62). This study showed that the herb was not only nephrotoxic, leading to end-stage renal disease in 43 patients, but was also a potent carcinogen.

Another recent case series identified 7 patients using a dietary supplement containing the herb yohimbine in addition to norephedrine, sodium usniate, caffeine, and 3,5-diiodothyronine (63). All patients developed acute hepatotoxicity within 3 months and all recovered spontaneously after this product was discontinued. Recent warnings from the German Federal Institute for Drugs and Medical Devices and the FDA describe an association between the popular herb kava and liver damage, including three cases leading to liver transplant and one case ending in death (64). A recent review of adverse events associated with the herb ephedra found that 31% of 140 cases, including 10 deaths and 13 cases of permanent disability, were definitely or probably related to the use of ephedra (65).

Side effects may also occur due to contaminants in herbal products. A study examining the contents of 260 Asian patent medicines found that 25% contained high levels of heavy metals, including lead, mercury, or arsenic, and another 7% contained undeclared pharmaceuticals, purposefully and illegally added to the herbs to produce a desired effect (66). PC-SPES, a popular herbal remedy that was initially believed to have promise in treating prostate cancer (67) has been found to contain varying amounts of the synthetic drugs diethylstilbestrol, indomethacin, ethinyl estradiol, and warfarin, which complicates investigations into whether the herb has any true anticancer effects (68).

Herbs may also interact with other drugs or other herbs. A recent systematic review of published herb-drug interactions found evidence of interactions with St. John’s wort, *G. biloba*, ginseng, garlic, and kava (Table 2) (69). Similarly, a review of herbal medicine use during the perioperative period identified several herbs that have the potential to interact with anesthetics and other medications commonly used during surgery (70). Specifically, garlic, *G. biloba*, and ginseng (often referred to as the “g” herbs) may increase the risk of bleeding during surgery; kava and valerian may increase the sedative effect of anesthetics; St. John’s wort has numerous reported drug interactions (Table 2); and ephedra has sympathomimetic activity that may increase the risk of cardiovascular adverse events (70). The majority of suspected herb-drug interactions are identified through case reporting (69), and it is therefore difficult to definitively determine if the herb-drug combination produced the observed side effect, or if patient characteristics or other factors were the causal factor. Few studies have examined herb-drug interactions, and therefore the risk of combining herbal products with prescription drugs is largely unknown. However, the potential for a substantial public health problem is clear: 16% of adults in the United States who report the use of one or more prescription drugs also take an herb or supplement preparation (71).

It is difficult to determine the true frequency of side effects from herbs, because surveillance systems are much less extensive than those in place for pharmaceutical drugs. The most important difference between reporting requirements for herbs and drugs is that herbal manufacturers are not required to “record, investigate, or forward” information to the FDA of reports or inquiries of adverse events associated with the use of their products (19). Similarly, adverse event reports of herbs may be limited because most patients do not discuss their use of herbs and other complementary and alternative medicine therapies with their physicians (1). If health care providers are not aware that their patients are using herbal products, they will not be able to discern or report a causal
relation between adverse events and herbs. A recent review conducted by the Office of the Inspector General concluded that surveillance systems designed to detect adverse reactions to herbs are inadequate and probably detect less than 1% of all events (72).

**Research and Future Directions**

Of the top 10 herbs sold in the United States, only four, garlic, *G. biloba*, saw palmetto, and St. John’s wort, are likely to be effective based on systematic reviews of randomized controlled trials. There is likely far less evidence available to evaluate the efficacy of the thousands of other single and multiherb products available in this country. This lack of evidence for efficacy is coupled with recent reports of serious side effects from herbal products (61–65) and a surveillance system that has been estimated to detect less than 1% of adverse reactions to herbs (72). Furthermore, two recent studies have shown that herbal product manufacturers frequently make unsubstantiated health claims or fail to disclose potential adverse effects or contraindications to herbal product use (17,73). Unfortunately, consumers are largely unaware of the limited regulation of herbal products. In a recent national telephone survey, 59% of adults in the United States incorrectly believed that a government organization was required to approve herbs and other supplements before they are sold (74).

Given the limited information about the efficacy of herbal products, the numerous concerns regarding safety, the reports of misleading labeling, and the ignorance of the public regarding product regulation, reform of the currently regulatory framework for herbs and supplements is urgently needed to protect consumers. Several authors have proposed regulatory changes, including requirements that all health claims be supported by data approved by the FDA, and that product labels provide an accurate list of all ingredients (16,75). Other proposed changes would require manufacturers to register with the FDA, conduct safety tests similar to those required for over-the-counter drugs, and forward all reports of adverse events associated with their products to the FDA (75). These regulatory changes should be complemented by improved surveillance systems and prospective studies designed specifically to detect adverse reactions to herbs, particularly in high-risk populations, including elderly patients, patients on multiple medications, and patients in the perioperative period.

Once the safety of the herbal product supply is established, research efforts can be directed towards characterizing and establishing standards for herbs and identifying herbal products that have efficacy for treating or preventing disease. Since approximately one third of drugs were derived from plant sources (12), it is likely that additional important therapies may be found from studying herbs. We believe that future investigations into the efficacy of herbal products should target both herbs with promising preliminary evidence of efficacy and conditions where standard medical therapies have failed to substantially improve patient outcomes. For example, it makes little sense to develop new herbal products to lower cholesterol

### Table 2. Published Herb-Drug Interactions with Commonly Used Herbs*

<table>
<thead>
<tr>
<th>Herb</th>
<th>Drug</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Garlic</td>
<td>Warfarin</td>
<td>Bleeding, increase in international normalized ratio</td>
</tr>
<tr>
<td></td>
<td>Chlorpropamide</td>
<td>Hypoglycemia</td>
</tr>
<tr>
<td><em>Ginkgo biloba</em></td>
<td>Warfarin</td>
<td>Bleeding</td>
</tr>
<tr>
<td></td>
<td>Aspirin</td>
<td>Bleeding</td>
</tr>
<tr>
<td></td>
<td>Thiazide diuretic</td>
<td>Increase in blood pressure</td>
</tr>
<tr>
<td></td>
<td>Trazodone</td>
<td>Increased sedation</td>
</tr>
<tr>
<td>Ginseng</td>
<td>Warfarin</td>
<td>Decrease in international normalized ratio</td>
</tr>
<tr>
<td></td>
<td>Phenelzine</td>
<td>Insomnia, headache, tremulousness, mania</td>
</tr>
<tr>
<td>Kava</td>
<td>Alprazolam</td>
<td>Sedation</td>
</tr>
<tr>
<td>St. John’s wort</td>
<td>Amitriptyline</td>
<td>Reduced plasma concentrations</td>
</tr>
<tr>
<td></td>
<td>Cyclosporine</td>
<td>Reduced plasma concentrations</td>
</tr>
<tr>
<td></td>
<td>Digoxin</td>
<td>Reduced plasma concentrations</td>
</tr>
<tr>
<td></td>
<td>Indinavir</td>
<td>Reduced plasma concentrations</td>
</tr>
<tr>
<td></td>
<td>Nefazodone</td>
<td>Symptoms of central serotonin excess</td>
</tr>
<tr>
<td></td>
<td>Oral contraceptives</td>
<td>Altered menstrual bleeding</td>
</tr>
<tr>
<td></td>
<td>Paroxetine</td>
<td>Symptoms of central serotonin excess</td>
</tr>
<tr>
<td></td>
<td>Phencoprocom</td>
<td>Reduced plasma concentrations</td>
</tr>
<tr>
<td></td>
<td>Sertraline</td>
<td>Symptoms of central serotonin excess</td>
</tr>
<tr>
<td></td>
<td>Theophylline</td>
<td>Reduced plasma concentrations</td>
</tr>
<tr>
<td></td>
<td>Warfarin</td>
<td>Decrease in international normalized ratio</td>
</tr>
</tbody>
</table>

* Herb–drug interactions were identified from a recently published systematic review (69).
levels, when very effective drugs with low toxicity currently exist (27,28). We also agree with the newly announced research priorities of the National Center for Complementary and Alternative Medicine, which have placed an increased emphasis on studies of the mechanism of action of herbs and other complementary and alternative therapies (76). These studies will provide new information about active ingredients, pharmacology, stability, and the bioavailability of herbs, all of which are essential for developing safe and effective products.

REFERENCES


