Dietary Supplements and Natural Products as Psychotherapeutic Agents

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Alternative therapies are widely used by consumers. A number of herbs and dietary supplements have demonstrable effects on mood, memory, and insomnia. There is a significant amount of evidence supporting the use of *Hypericum perforatum* (St. John's wort) for depression and *Ginkgo biloba* for dementia. Results of randomized, controlled trials also support the use of kava for anxiety and valerian for insomnia. Although evidence for the use of vitamins and amino acids as sole agents for psychiatric symptoms is not strong, there is intriguing preliminary evidence for the use of folate, tryptophan, and phenylalanine as adjuncts to enhance the effectiveness of conventional antidepressants. *S*-adenosylmethionine seems to have antidepressant effects, and omega-3 polyunsaturated fatty acids, particularly docosahexaenoic acid, may have mood-stabilizing effects. More research should be conducted on these and other natural products for the prevention and treatment of various psychiatric disorders. **Key words:** *Ginkgo biloba*, kava, St. John's wort, vitamins, dietary supplements, omega-3 fatty acids.

ADAS-Cog = Alzheimer's Disease Assessment Scale–Cognition subscale; CAM = complementary and alternative medicine; cAMP = cyclic adenosine monophosphate; DHA = docosahexaenoic acid; DSM = *Diagnostic and Statistical Manual of Mental Disorders* (3rd, 3rd revised, and 4th editions); EMS = eosinophilia-myalgia syndrome; EPA = eicosapentaenoic acid; GABA = γ-aminobutyric acid; HAM-A = Hamilton Anxiety Rating Scale; HAM-D = Hamilton Depression Rating Scale; ICD = International Classification of Disorders; MAO = monoamine oxidase; OCD = obsessive-compulsive disorder; PAF = platelet-activating factor; PUFA = polyunsaturated fatty acids; SAMe = *S*-adenosylmethionine; SJW = St. John's wort; SRI = serotonin reuptake inhibitor; UV = ultraviolet; 5-HTP = 5-hydroxytryptophan.

INTRODUCTION

Complementary and alternative medicine (CAM) is popular in the United States, and interest in CAM therapies seems to be growing. A telephone survey of 2055 adults found that 42% of U.S. consumers used CAM therapy in 1997, up from 34% in 1990 (1). Herbal medicine use rose from 3% to 12%, and use of high-dose vitamins rose from 2.4% to 5.5% during this period. Other findings of note included the following: the majority of consumers use CAM therapies for chronic rather than life-threatening medical conditions, most users of alternative therapies do not inform their primary care physicians of such use, and out-of-pocket expenditures associated with CAM therapies are roughly equivalent to out-of-pocket expenses for hospitalizations.

Results of another survey of 1035 consumers who had previously responded to a mail survey confirm those of the above-mentioned study: 40% of respondents reported use of alternative health care during 1996 (2). Higher educational attainment and less-than-optimum health status were predictors of who was likely to use alternative medicine; negative experiences with conventional medicine were not predictive of alternative health care use. Use was found across all racial, ethnic, income, and age groups and was equivalent between men and women. The most frequently cited health problems treated with alternative therapies were chronic pain (37%), anxiety (31%), chronic fatigue syndrome and "other health conditions" (31%), sprains and muscle strains (26%), addiction (25%), arthritis (25%), and headaches (24%).

Psychiatric conditions apparently are often a target of treatment; anxiety and depression were among the most common conditions treated with CAM therapies in both the Eisenberg et al. (1) and Astin (2) surveys. At the 1998 New Clinical Drug Evaluation Unit annual meeting, it was reported that 56% of 150 subjects screened at the Medical University of South Carolina clinic had used herbal medicines within the previous month (3). Forty-eight subjects had used herbs to treat psychiatric symptoms (56% reported a positive response), and 50 had used herbs to treat nonpsychiatric symptoms (52% reported a positive response).

The National Institutes of Health Office of Alternative Medicine and the National Institute of Mental Health have jointly designed and funded a $4.3 million clinical trial to determine the efficacy of SJW in major depression. Although SJW is undoubtedly a popular botanical product (resulting in $48 million in US sales for 1997), other herbs are important both clinically and economically (4). In 1997, ginkgo (used for senile dementia or benign forgetfulness) generated US sales of $90 million; and ginseng (used to increase energy levels and vigor) had a market of $86 million.

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Received for publication July 30, 1998; revision received March 1, 1999.

0033-3174/99/6105-0712

Two agents used for relief of stress and anxiety include kava (with sales of $2.9 million) and valerian (with sales of $6.1 million). Besides herbs, consumers use a variety of nutritional supplements (including vitamins, amino acids, and fish oil) that may affect mood and functioning.

Many herbal, nutritional, and combination products are available at pharmacies. The majority of those who use herbal and high-dose vitamin products do so without consulting either a physician or a CAM provider, and almost one in five prescription drug users are also using herbs and/or high-dose vitamin supplements (1). This raises the concern of herb-drug and nutrient-drug interactions, about which little is known.

It is important for clinicians to be aware of the data available on dietary supplements that consumers are using. This article summarizes the current knowledge on major botanicals and nutritional supplements with purported psychotherapeutic effects.

HERBS

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

SJW is a common roadside plant (Figure 1, *A*) that has gained much popularity in the United States as an antidepressant (5, 6). Hypericum seems to be an effective antidepressant with an excellent safety profile, but more information is needed on its efficacy compared with SRIs. A MEDLINE search for "St. John's wort" produced 1547 publications, and a search for "hypericum" produced 141 publications.

Many studies have been performed on this herb in Europe, primarily Germany. A recent meta-analysis evaluated 23 randomized trials (20 were double blind) of SJW in a total of 1757 outpatients with mild to moderate depression (7). Improvement in depressive symptoms (usually measured by the HAM-D or Clinical Global Impression scale) was observed in all groups. In 15 placebo-controlled trials, SJW was found to be significantly more effective than placebo. In eight treatment-controlled trials, clinical improvement in those receiving SJW did not differ significantly from those receiving tricyclic antidepressants.

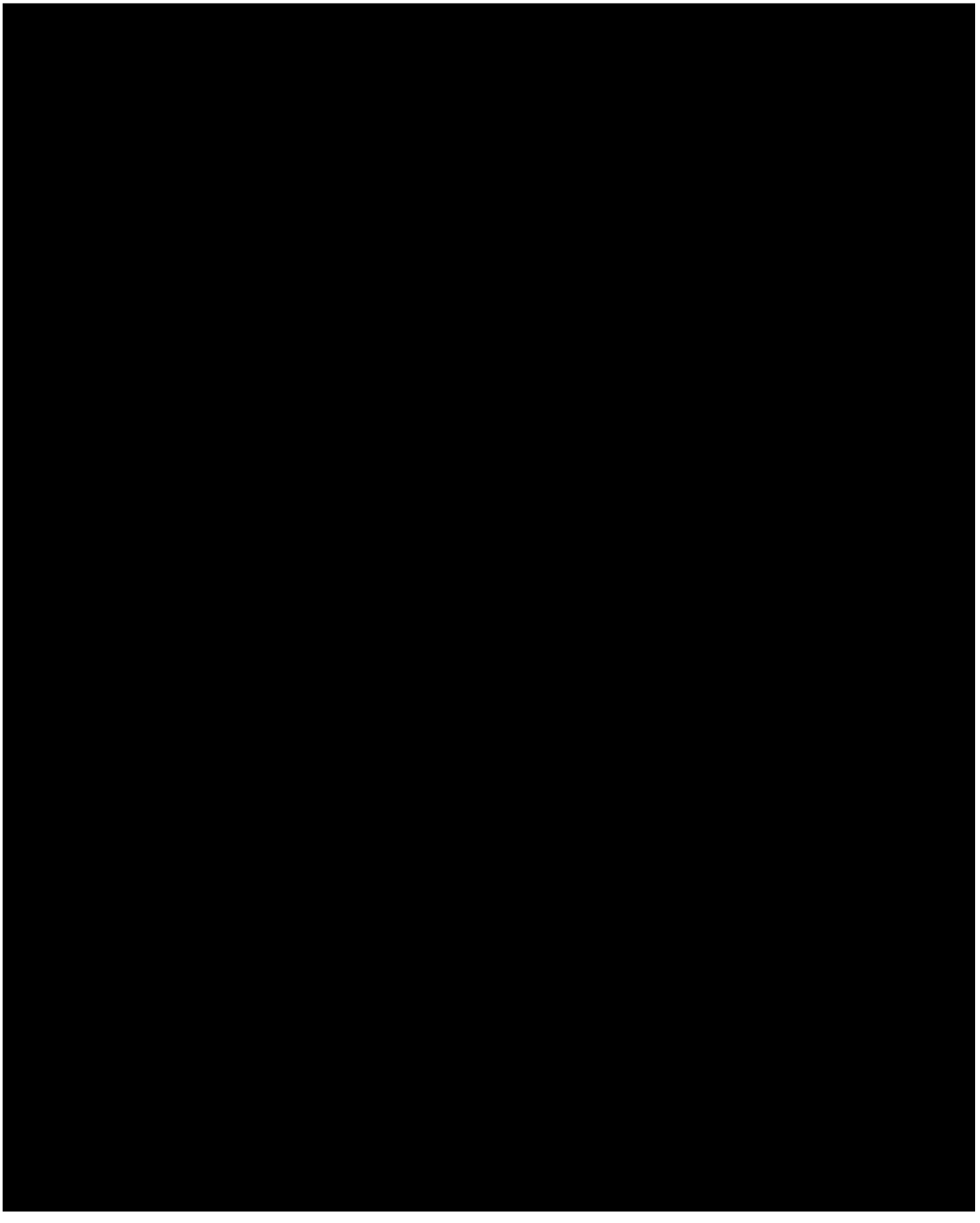
Most trials were 4 to 8 weeks in duration. The trials in this meta-analysis were heterogenous and used various diagnostic criteria and dosages of herb. In 20 trials, single-herb preparations were tested; the remainder tested combination herb products. Thirteen trials compared a single hypericum preparation with placebo and provided data on treatment responders; of these, 55.1% of those receiving the herb improved, compared with 22.3% of those receiving placebo. No significant differences in treatment effect were found between single-herb preparations of SJW and standard antidepressants. Combination products (containing both hypericum and the sedative herb valerian) also were not significantly different from standard antidepressants. Side effects were reported less often with SJW; 19.8% of those on SJW reported symptoms, compared with 52.8% of those on tricyclic antidepressants.

Diagnostic criteria for depression also differ in Germany, and most of the SJW trials used ICD-9 diagnostic criteria (a few used ICD-10 or DSM-IV criteria). There are no clinical trials comparing SJW to SRIs. In Germany, SRIs became popular only recently; at the time that most SJW studies were performed in Germany, the usual treatment for depression was small doses of tricyclic antidepressants (eg, 75 mg/d imipramine). Whether SJW compares favorably with SRIs in terms of therapeutic benefit and side effects remains to be determined.

One 6-week trial from the United Kingdom (8) using DSM-IV criteria found that the proportion of patients responding to a daily dose of 75 mg of amitriptyline (34 of 78) was similar to those responding to 900 mg of hypericum (37 of 87), but by the end of the study, the total decrease in depression scores favored amitriptyline. Another 6-week trial in 209 more severely depressed patients examined the effects of larger doses of each medication (9). HAM-D scores in those receiving hypericum (1800 mg/d) decreased from 25.3 to 14.4, and in the imipramine (150 mg/d) group, scores decreased from 26.1 to 13.4. Although there was a small advantage for the tricyclic antidepressant over hypericum in both trials, fewer adverse effects were reported with SJW.

The National Institutes of Health National Center for Complementary and Alternative Medicine and National Institute of Mental Health recently contracted with Duke University to conduct a multicenter study comparing SJW with sertraline (Zoloft) and placebo in patients diagnosed with major depression.

Although SJW demonstrates MAO inhibition in vitro, this effect has not been demonstrated in vivo, nor have there been any reported cases of MAO inhibitor–associated hypertensive crises in humans using SJW (7). Although SJW inhibits serotonin, norepinephrine, and dopamine in vitro (10), the concentrations required to attain these effects are quite high and render the chances of attaining equivalent blood concentrations unlikely. The most potent effect of SJW seems to be on $GABA_A$ and $GABA_B$ receptors, with a median inhibitory concentration of 60 ng/ml for $GABA_A$ and 9 ng/ml for $GABA_B$ (11). Recent data suggest that a component of the extract called hyperforin may be more



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important to the therapeutic activity than hypericin (by which it is standardized) (12).

Adverse Effects and Interactions. Side effects reported for SJW are generally mild. Gastrointestinal symptoms and fatigue have been reported (7). The most predictable effect seems to be photosensitization, especially in fair-skinned people. First noted in light-skinned cows that grazed in pastures in which SJW grew, photosensitization has been demonstrated in a controlled clinical trial involving hypericin and exposure to metered doses of UVA and UVB irradiation (13). Using LI 160, a standardized extract from Lichtwer Pharma (Berlin, Germany), these authors found a measurable increase in erythema in light-sensitive volunteers exposed to UVA irradiation after receiving 600 mg of SJW three times daily for 15 days. This effect has also been seen in humans taking high doses of synthetic hypericin (14). Photosensitization is generally mild and transient, disappearing within a few days of drug discontinuation. Although this effect is usually associated with higher than recommended doses of hypericum, it can occur at lower doses and generally appears on the package labeling as a precaution. No other adverse effects were observed in the high-dose studies.

There have been several case reports of unusual reactions to SJW. One unusual case report of excessive sedation describes a 50-year-old woman with asthma and depression who discontinued the SRI paroxetine (40 mg/d) and began taking SJW (600 mg/d) (15). Ten days after switching medications, she took 20 mg of paroxetine at bedtime and was found lethargic and incoherent in the morning. On examination later the same day, her vital signs and results of physical examination, Mini Mental Status examination, blood chemistry workup, and complete blood count were all normal. The only symptoms were slow response time and limp muscle tone; the patient was completely back to baseline by the next day. This case is difficult to interpret because no adverse signs or symptoms were evident during an examination performed the same day. Also, neither paroxetine nor SJW is particularly sedative.

A case of adynamic ileus was reported in a 67-year-old woman with diabetes (controlled by glyburide and diet) who began taking SJW 2 weeks before her symptoms developed (16). Her condition resolved with conservative treatment and discontinuation of SJW.

There are two unpublished case reports of possible mild "serotonin syndrome," characterized by mental confusion, muscle twitching, sweating, flushing, and ataxia, in patients consuming SJW (17). In one case, the patient was taking SJW alone; in the other, the patient had also been taking trazodone.

One case of acute neuropathy was reported (18) in a 35-year-old woman who developed stinging pain in the face and hands after exposure to the sun. She had been taking SJW (500 mg/d) for 4 weeks before the development of symptoms. After withdrawal of SJW, symptoms began to clear after 3 weeks and were gone by 2 months. The author attributed these effects to the photosensitizing properties of SJW.

Animal studies indicate low toxicity for SJW. Rats fed SJW as 5% of their diet for 119 days experienced no adverse effects on the liver or any significant tissue lesions (19). Hepatic enzymes were induced, an effect that could theoretically increase metabolism and decrease bioavailability of drugs metabolized by those hepatic enzymes.

In chronic toxicity studies in rats and dogs, only nonspecific symptoms of toxicity were seen, including reduced body weight, slight pathological changes in liver and kidneys (most likely due to increased metabolic load), and some histopathologic changes in the adrenal glands (20). No effects on fertility or reproduction were observed. No mutagenic potential was evident. Long-term (≈2 years) carcinogenicity studies were recently completed, but the results have not been reported.

Ginkgo (*Ginkgo biloba*)

Ginkgo leaf extracts, containing 120 to 240 mg of standardized extract, may be helpful for treating memory problems and dementia (Figure 1, *B*). However, ginkgo seems to have anticoagulant effects, and caution should be used in patients with clotting disorders or who are receiving anticoagulant therapy.

Ginkgo is one of the world's oldest species. It is a decorative tree often planted in cities because of its resistance to pollution, insects, and disease. The use of ginkgo has greatly increased since 1994, when the German government approved a standardized form of leaf extract (EGb761) for the treatment of dementia. The standardized extract contains 22% to 27% flavonoid glycosides (including quercetin, kaempferol, and their glycosides) and 5% to 7% terpene lactones (consisting of 2.8–3.4% ginkgolides A, B, and C and 2.6–3.3% bilobalide) (21). A recent MEDLINE search produced 434 references for the term "ginkgo."

A randomized, double-blind, placebo-controlled trial of 309 patients with Alzheimer's or multiinfarct dementia found that patients receiving 120 mg of ginkgo extract (EGb 761) daily scored higher on the ADAS-Cog, a performance-based cognitive test (22). After 1 year of treatment, 29% of patients receiving ginkgo showed at least a four-point improvement on the test, compared with 14% of those receiving pla-

cebo. This difference is comparable to achieved with high-dose tacrine, which resulted in a four-point improvement in 40% of those receiving the drug vs. 25% of patients receiving placebo (23). Although this may seem unremarkable to those unfamiliar with the ADAS-Cog, four points is the average amount of decline normally seen in Alzheimer patients over a 6-month period, so a four-point improvement is clinically significant. Although improvement was not apparent in the Clinician's Global Impression of Change scale, beneficial treatment effects were apparent to caregivers, as measured by the Geriatric Evaluation by Relative's Rating Instrument.

A randomized, double-blind, placebo-controlled trial of 216 patients with Alzheimer's or multiinfarct dementia found that 240 mg/d for 6 months of a standardized ginkgo extract resulted in significant improvements in memory, attention, psychopathology, and behavior compared with placebo (24).

Another randomized, double-blind, placebo-controlled trial of 40 Alzheimer's patients, half of whom were given 240 mg/d of standardized ginkgo extract for 3 months, found significant improvements in memory, attention, and psychopathology in the group receiving ginkgo after 1 month (25).

Ginkgo may also have beneficial effects on memory impairment. A double-blind study of 31 outpatients older than 50 years with mild to moderate memory impairment found a beneficial effect with 120 mg/d on some tests (eg, digit copying and speed of response in a classification task) but not others of cognitive function at both 12 and 24 weeks (26).

A recent meta-analysis by Oken et al. (27) attempted to summarize the results of all published studies in which ginkgo was given for dementia. Trials included in the meta-analysis were randomized, double blind, and placebo controlled. Patients were sufficiently characterized with a diagnosis of Alzheimer's disease by either DSM-III or National Institute of Neurological Disorders and Stroke–Alzheimer's Disease and Related Disorders Association criteria, or enough clinical data were available for the reviewer to assign a diagnosis. Patients with depression or other neurological disease and those using central nervous system–active medications were excluded. The trials included use of standardized ginkgo extract at any dose, had at least one outcome measure that was an objective assessment of cognitive function, and contained sufficient statistical information for meta-analysis. Although more than 50 articles were identified, the majority did not meet inclusion criteria because of a lack of clear diagnoses of dementia and Alzheimer's. In the four studies meeting all inclusion criteria, there were a total of 212 subjects each in the placebo and ginkgo treatment groups. Overall, there was a significant effect ($p < .0001$) that translated into a 3% difference in the ADAS-Cog score. The authors concluded that there is a small but significant effect of 3 to 6 months of treatment with 120 to 240 mg of ginkgo biloba extract on objective measures of cognitive function in Alzheimer's disease. Additional research was recommended to determine whether there are functional improvements and to determine the best dosage.

A meta-analysis of 40 controlled trials for "cerebral insufficiency" (an ill-defined syndrome encompassing difficulties of memory and concentration, confusion, fatigue, depression, tinnitus, and headache) has also been performed (28, 29). The meta-analysis found that in 26 studies, the group receiving ginkgo did significantly better than the control group; in 13 studies, there was a trend toward a benefit or a benefit for some but not all effect measurements. Most of the studies were deemed to be of poor methodological quality. Of the eight well-performed trials, all showed a significant benefit for the ginkgo group (28, 29). Electroencephalographic changes after acute administration of ginkgo extract are unique among psychoactive drugs and are consistent with effects seen with other nootropic agents (30, 31).

There are several mechanisms by which ginkgo may improve mental performance and behavior in patients with dementia. These effects are most likely synergistic. Reputed to increase blood flow through small vessels (including cerebral arteries), ginkgo seems to have vasoregulatory effects and to inhibit platelet aggregation (29). EGb 761 and/or other more purified extracts (ginkolides or bilobalides) increase tolerance to hypoxia (32, 33), are neuroprotective (34–36), inhibit phospholipase A (37), and stabilize membranes and decrease capillary fragility (38, 39). EGb 761 also acts as an antioxidant (40, 41) and increases cerebral blood flow and enhances utilization of oxygen and glucose (21, 42). Other actions include inhibition of PAF (43, 44), lipid peroxidase (21), and protein kinase C (45). Thus, to various degrees, the active constituents in ginkgo act as scavengers for free radicals (21, 46, 47), which have been considered the mediators of the excessive lipid peroxidation and cell damage observed in Alzheimer's disease (48–51).

Adverse Effects and Interactions. In humans, side effects are rare. In a German postmarketing surveillance study of 10,815 patients treated with LI 1370 (another brand of standardized ginko), only 183 reported side effects. These included nausea (37), headache (24), stomach problems (15), diarrhea (15), allergy (10), anxiety or restlessness (8), sleep disturbances (6), and other (68).

Although it may be a component of its therapeutic

activity, ginkgo does have anticoagulant effects and, in rare cases, has been associated with serious bleeding problems. There have been five reports of bleeding associated with ginkgo treatment. These include two subdural hematomas, one with a documented increase in bleeding time (52, 53); one intracerebral hemorrhage (54); and one subarachnoid hemorrhage (55). There was also one case of hyphema (56). In most cases, patients were receiving concurrent anticoagulant drugs. All patients seem to have recovered with no sequelae. Ginkgo reduces platelet aggregation by inhibiting PAF, and concurrent use of anticoagulants and ginkgo extracts should probably be avoided. It should also be avoided in patients with clotting problems.

The toxicity of ginkgo leaf extracts is very low. Tests in mice showed a median lethal dose of 7725 mg/kg PO and 1100 mg/kg IV. An acute median lethal dose could not be determined in rats. Results of tests for mutagenicity, carcinogenicity, and genotoxicity were negative (57).

Ginkgo fruit pulp is quite potent as a contact sensitizer. It is possible that there is cross-reactivity between ginkgo fruit and the poison ivy-oak-sumac family (58).

Kava (*Piper methysticum*)

Widely used in Polynesia, Micronesia, and Melanesia as a ceremonial, tranquilizing beverage, kava, a psychoactive member of the pepper family, is used medicinally for anxiety and insomnia in Europe and the United States (Figure 1, *C*). It is approved in Germany for "states of nervous anxiety, tension, and agitation" in doses of 60 to 120 mg of kavalactones for up to 3 months (59, 60). Kava seems to be a safe herb for short-term relief from stress and anxiety. A MEDLINE search for "kava" produced 78 publications. Several placebo-controlled trials have shown significant anxiolytic activity. The principal ones are mentioned briefly.

In a randomized, double-blind, placebo-controlled trial, 58 patients with various ICD-diagnosed anxiety and neurotic disorders were randomly assigned to receive 70 mg of kavalactones from extract WS 1490 (Laitan) or placebo three times daily for 4 weeks. Compared with the placebo group, the kava group demonstrated a significant reduction in anxiety (assessed by HAM-A) by the end of the first week; differences between the two groups increased during the course of the study. Side effects were minimal, with the authors reporting "no undesirable events" (61).

In a randomized, double-blind, placebo-controlled multicenter study, 101 outpatients with DSM-III-R anxiety disorders (agoraphobia, specific phobia, generalized anxiety disorder, or adjustment disorder with anxiety) were treated with the kava extract WS1490 (210 mg/d in divided doses) for 24 weeks (62). Results showed significant reductions in HAM-A scores in the kava group beginning in the eighth week and increasing throughout the trial. Improvements were also seen in secondary outcome variables, which included Hamilton subscale scores for somatic and psychic anxiety, the Clinical Global Impression scale, Self-Report Symptom Inventory, and the Adjective Mood scale. Side effects were greater in the placebo group than the kava group, the latter consisting of two patients with upset stomach. No changes were observed in clinical blood chemistry values, hematological parameters, or vital signs. In contrast to the benzodiazepines and tricyclics, both of which are used to treat anxiety disorders, treatment with kava did not lead to tolerance.

Several other controlled double-blind trials on kava extracts or the isolated compound DL-kawain have been published in the German literature (59). In one placebo-controlled trial, 58 patients with anxiety received 210 mg of kava or placebo daily for a month (63). Compared with patients receiving placebo, those receiving kava had significantly greater reductions in HAM-A scores with improvements beginning within 1 week.

In a treatment-controlled trial with the same entry criteria as used in the Lehmann et al. (61) trial, a daily dose equivalent to 210 mg of kavapyrones was compared with 15 mg/d oxazepam or 9 mg/d bromazepam for 6 weeks. In the 164 patients who completed the protocol, HAM-A scores did not differ significantly among the three groups (64).

In a placebo-controlled, double-blind clinical trial, 38 outpatients with anxiety associated with neurotic or psychosomatic disturbances were treated with DL-Kavain (Neuronika) or oxazepam (65). The anxiolytic effectiveness of the two preparations was judged by means of the Anxiety Status Inventory and the Zung Self-Rating Anxiety Scale to be equivalent. No adverse drug reactions were reported.

A study of kava for climacteric symptoms in 40 women using doses of 30 to 60 mg/d for a minimum of 56 days found significant improvements in the HAM-A score and Kupperman index (66). In a follow-up study in 40 women taking 210 mg/d, similar anxiolytic effects were reported (67).

In 12 healthy volunteers, a kava extract (200 mg) was compared with a high dose of oxazepam (75 mg) in a double-blind crossover study that evaluated event-related potentials and recognition memory (68). Although oxazepam predictably impaired both parameters, kava slightly enhanced both.

Kava is one of the few herbs for which active constituents are well delineated; these are the kavapyrones, including kawain, dihydrokawain, methysticin, and dihydromethysticin (59). The kavapyrones are centrally acting skeletal muscle relaxants and anticonvulsants. Their effects seem to be due to inhibition of sodium and calcium channels as well as effects on glutamate systems (69). Kava extract has been reported to affect $GABA_A$ receptors, as shown by enhanced muscimol binding (70), but has also been reported to have no effect on GABA or benzodiazepine binding (71). Several kavapyrones, including methysticin and dihydromethysticin, are potent inhibitors of norepinephrine uptake (72).

Adverse Effects and Interactions. Therapeutic doses may result in mild gastrointestinal complaints or allergic skin reactions (incidence, 1.5%) (59). Chronic use of kava up to 100 times the therapeutic dose (73) results in an ichthyosiform eruption known as kava dermopathy, which is often accompanied by eye irritation (74). This scaly dermatitis is similar to that seen in pellagra, but niacin deficiency is apparently not the mechanism, because a randomized controlled trial of administration of 100 mg of nicotinamide in 29 habitual kava drinkers with dermopathy showed no difference between the treatment and placebo groups (75). Abstaining from kava results in complete resolution of symptoms.

Interaction studies with alcohol found differing effects in humans and animals. A synergistic effect was reported in mice using hypnotic doses of kava and alcohol (76). However, a clinical trial in 20 volunteers (77) given 100 mg of kava extract three times per day for 8 days tested the added effects of alcohol by adding ethanol on days 1, 4, and 8 (doses of alcohol were sufficient to achieve blood alcohol levels of 0.05%). This study showed no additive effects of alcohol with kava.

Kava may interact with benzodiazepine metabolism. A 54-year-old man on daily doses of alprazolam, cimetidine and terazosin was hospitalized after experiencing an acute change in mental status 3 days after starting to take kava (78). He recovered from his lethargy and disorientation within several hours. (It is worth noting that this may have been a multiple drug interaction; cimetidine can decrease metabolism of a number of drugs and may have contributed to this adverse reaction.)

A study in mice showed no apparent development of tolerance to doses of 100 mg/kg for 7 weeks and only a slight tolerance at doses of 150 mg/kg (79). Kava extracts have been tested in formal chronic (26-week) toxicity studies in rats (up to 320 mg/kg) and dogs (up to 60 mg/kg). The high dose resulted in only mild histopathological changes in liver and kidneys. There has been no evidence of mutagenic, teratogenic, or genotoxic potential in standard assays (73).

Ginseng (*Panax ginseng* and others)

Ginseng is a popular "tonic" herb (one meant to be taken regularly that has cumulative strengthening effects) (Figure 1, *D*). There are several varieties of ginseng. The three *Panax* species commonly used in herbal medicine are *P. ginseng*, grown in northeastern China and Korea; *P. quinquefolius*, grown in the United States and Canada; and *P. notoginseng*, grown in southwest China. "Siberian ginseng" is not ginseng at all, although it is in the same family (Araliaceae) and is also used for its tonic effects.

Ginseng has many interesting effects, but its place in the treatment of psychiatric conditions or improving quality of life has yet to be demonstrated in clinical trials. An 8-week, placebo-controlled study of a commercial ginseng-multivitamin/multimineral preparation among 60 patients admitted to the geriatric unit of a hospital found no differences between the two groups in length of stay, activities of daily living, cognitive function, or somatic symptoms (80). A double-blind study of a multivitamin complex supplemented with ginseng vs. a multivitamin complex without ginseng in 625 patients complaining of stress or fatigue found significant improvement in the quality of life index at 4 months in those receiving ginseng (81).

The actions of ginseng are complex. Ginseng contains ginsenosides (triterpene saponins), polyacetylenes (ginsenoynes A–K), and sesquiterpenes. It seems to have corticosteroid-like actions and hypoglycemic activity and also affects neurotransmitter activity (58). A ginsenoside extract from *P. ginseng* demonstrated affinity for progestin, mineralocorticoid, and glucocorticoid receptors in vitro (82). In rats, ginseng saponins increase adrenocorticotropic hormone and corticosterone secretion (83). Glucocorticoid administration blocks the effect of ginsenosides both in vitro and in vivo; ginsenosides increase adrenal cAMP in intact but not hypophysectomized rats, so effects on adrenal secretion seem to be due to an effect on the pituitary gland (58). Ginseng inhibits platelet aggregation; a nonsaponin (lipophilic) fraction potently inhibits thromboxane A2 production without affecting cAMP formation (84). In rat brain tissue, ginseng inhibits the uptake of neurotransmitters, including GABA, norepinephrine, dopamine, glutamate, and serotonin (58, 85) (however, it is not clear whether ginseng actually enters the brain). The pharmacokinetics of ginseng have not been well delineated.

Adverse Effects and Interactions. Ginseng can cause estrogenic effects even though it does not actually contain phytoestrogens. Two cases of postmenopausal uterine bleeding have been reported. One occurred in a patient who ingested a geriatric formula containing ginseng (86); another occurred in a 44-year-old postmenopausal woman after use of a face cream that contained ginseng (87). Follicle-stimulating hormone levels rose to normal postmenopausal levels after use of the face cream was discontinued. Three weeks after rechallenge, the level of follicle-stimulating hormone dropped from 70 to 27 mIU; 1 week later another episode of uterine bleeding occurred. One case of swollen breasts and diffuse nodularity was reported in a 70-year-old woman (88). The symptoms disappeared on discontinuation of the ginseng and recurred on rechallenge. Another report of five cases of mastalgia lacks detail and thus is unevaluable (89).

Two cases of possible interactions between ginseng and phenelzine (Nardil) have been described. In the first case, a 64-year-old woman developed headache and tremor after consuming the two together (90); in the second case, a 42-year-old woman with a history of unipolar depression experienced what seemed to be a manic reaction to the combination of ginseng and bee pollen with phenelzine (91). In neither case was the ginseng preparation analyzed to ensure that ginseng was actually present. A number of purported ginseng products contain no ginseng and may contain other herbs, such as ephedra (92).

Passionflower (*Passiflora incarnata*)

Passionflower is used as a mild sedative, often in combination with other herbs (Figure 1, *E*). It seems to be safe. No clinical trials of its use as a single agent have been conducted. The German Commission E recommends 4 to 8 g of dried herb per day for "nervous unrest."

In a double-blind trial in 182 patients with adjustment disorder with anxious mood, patients received a preparation containing six extracts (*Passiflora*, *Crataegus*, *Ballota*, *Valeriana*, *Cola*, and *Paullinia*) or placebo. HAM-A scores were improved in patients who took the herbal mixture compared with those who received a placebo (93).

Passionflower contains flavonoids, mainly C-glycosides of apigenin and luteolin, maltol, essential oil, and gynocardia, a cyanogenic glycoside. It is not clear what components of the plant are responsible for its sedative effects. It has been reported that chrysin (5,7-dihydroxyflavone), a flavonoid derived from *Passiflora coerulea*, is a partial agonist of benzodiazepine receptors and has anxiolytic activity in mice without inducing sedation or muscle relaxation and could account for the activity of the plant (94). No information on pharmacokinetics is available.

Adverse Effects and Interactions. No adverse reactions have been reported, besides one unconvincing case of hypersensitivity vasculitis. A hypersensitivity reaction with urticaria and a blistering rash with the clinical appearance of cutaneous vasculitis (no biopsy was done) was reported in a 77-year-old man with rheumatoid arthritis. He was also taking diclofenac and cyclopenthiazide (both of which he had taken for years and remained on during resolution of the rash) (95). This may have been an interaction effect, and although a rash clearly occurred, the diagnosis of vasculitis was not proven.

No acute toxicity was observed in mice given up to 900 mg/kg IP (96). In rats, 21 days of oral treatment with 10 ml/kg (equivalent to 5 g/kg) of a hydroethanolic extract of *Passiflora* had no effect on surface or deep electroencephalography, body weight, rectal temperature, tail flick, or motor coordination. There was, however, a reduction in general motor activity (97).

Skullcap *(Scutellaria laterifolia)* Labiatae

This common plant (also called helmet flower, hoodwort, and mad-dog weed) is native to the United States (Figure 1, *F*). Related species are found in Europe and Asia and are common ingredients in many Chinese herbal formulas used for a variety of indications, including inflammation, dermatitis, allergic diseases, hyperlipidemia, chronic hepatitis, and atherosclerosis (58). Although a recent MEDLINE search produced 92 publications on *Scutellaria*, most were in Chinese, Russian, and Japanese and dealt with non–central nervous system effects of other species, particularly *S. baicalensis*. Little research has been conducted on *S. laterifolia* (probably because it is found only in the United States) or the central nervous system properties of the plant, which include antispasmodic, diuretic, sedative, and tonic effects (98). It is said to be good for spasms, convulsions, delirium tremens, nervous conditions of all sorts, and even rabies (hence the name mad-dog weed) in a dose equivalent to 1 to 2 g of dried herb. The primary active constituents are thought to be scutellarin, other flavonoid glycosides, and flavones (58). It is often combined with valerian and/or passionflower.

Adverse Effects and Interactions. Although there are no known specific toxic effects or contraindications, overdosage is said to produce giddiness, stupor, confusion, and seizures (58). Liver toxicity has been reported with preparations labeled as containing skullcap (99). However, adulteration with the hepatotoxic

plant *Teucrium chamaedrys* has been reported to commonly occur in the United Kingdom and was found to be the offender in at least one case (100).

Valerian (*Valeriana officinalis*)

Valerian is an odoriferous, popular European botanical medicine used for its mild sedative and tranquilizing properties (Figure 1, *G*). This common herb is native to Europe and Asia and now grows in most parts of the world. The central nervous system activity is largely ascribed to the valepotriates and sesquiterpene constituents of the volatile oils. Many formulations are marketed (about 80 in the United Kingdom), and it is usually standardized according to the content of volatile oil and valerenic acid. The German Commission E recommends 2 to 3 g of the dried root one or more times a day for "restlessness and nervous disturbance of sleep" (101). Valerian is a popular sleep remedy even though few clinical trials on sleep or other parameters can be found in the literature (102). A MEDLINE search for "valerian" produced 177 publications.

In one study in 166 subjects, a commercial herbal formulation containing *Valeriana officinalis* as one of a mixture of herbs was compared with a valerian-only aqueous extract (400 mg) and placebo in subjects with various sleep difficulties (103). Each person received three of each capsule, which were taken in random order on nonconsecutive nights. Only 128 patients completed the study; of the others, most were administrative dropouts (moved away, etc.). Only one patient withdrew because of side effects. Both valerian preparations produced a significant decrease in subjectively evaluated sleep latency scores and improved sleep quality. Night awakenings and dream recall were not affected by valerian, nor did valerian cause any somnolence the next morning. In another study, 27 patients with sleep difficulties received two tablets that were taken on two consecutive nights, one on each night (104). Both preparations contained hops and lemon balm, but one contained 4 mg of valerian, and the other contained 400 mg (full dose). (Although both hops and lemon balm are mild sedatives, valerian is considered to be more effective.) Seventy-eight percent of subjects preferred full-dose valerian, 15% preferred the low-dose valerian, and 7% had no preference.

A study in which 10 normal subjects took a single dose of valerian at home and 8 subjects took valerian in a sleep laboratory found that under home conditions, either 450 or 900 mg of freeze-dried aqueous extract reduced perceived sleep latency and wake time after sleep onset (105). In the sleep laboratory, the effects of 900 mg of valerian were not significantly different from those of placebo, a finding the researchers suggest may be explained by the stressful sleep environment obscuring the mild hypnotic action of valerian. A small study of 14 elderly poor sleepers found that 405 mg of dried aqueous valerian had no effect on sleep onset time or time awake after sleep onset in 8 subjects who received valerian as compared with 6 subjects who received placebo (106). Those in the valerian group, however, did exhibit an increase in slow wave sleep and a decrease in sleep stage I.

A recent open-label study of valerian and insomnia enrolled 23 symptomatic Hispanic men and women (107). Eleven of the volunteers were diagnosed with major depression, four with generalized anxiety, two with schizoaffective disorder, two with primary sleep disorder, and one with dysthymia. The primary outcome was the score on a self-rated ordinal scale symptom questionnaire completed at baseline and at the end of weeks 1 and 2. Participants were given a bottle of a local brand of valerian capsules (Natures Way, 530 mg valerian root) and instructed to take one each night 30 to 60 minutes before retiring. They were allowed to increase to two capsules after the third night and to three capsules after the first week. Three patients failed to return to the first-week appointment, but the remaining 20 completed the 2-week study. Sixteen patients rated themselves as at least moderately improved at the end of week 1. At the end of week 2, most patients described the medication as extremely helpful. No side effects were reported, and most participants said they would purchase this product themselves if their insomnia continued or reoccurred. The authors concluded that valerian was effective over this 2-week period and recommended that additional controlled trials be performed. The distinctive odor of valerian may present difficulties in designing a plausible placebo for a controlled trial.

A study of valerian and propranolol on activation, performance, and mood under social stress found that propranolol prevented physiological activation, whereas valerian decreased subjective feelings of somatic arousal without affecting physiological activation. The two drugs act independently of each other, and no interaction was observed when the two drugs were used together (108).

The essential oil of valerian contains monoterpenes and sesquiterpenes. A valerian root extract high in the valepotriate valtrate exhibited interaction with adenosine receptors. The components hydroxyvalerenic acid and acetoxyvalerenic acid can inhibit the breakdown of GABA (96).

Valerenic acid has been reported to inhibit the catabolism of GABA in vitro (109). In other in vitro studies, extracts of valerian showed affinity for rat brain $GABA_A$ and barbiturate receptors (110). The high

concentrations of the amino acids, GABA and/or glutamate, in valerian extracts have been suggested to account for much of its pharmacology (111). To date, however, no compelling cases have been made for either a mechanism of action or for active constituents.

Adverse Effects and Interactions. The median lethal dose of an alcoholic extract of valerian in mice has been reported to be 3.3 g/kg IP (96). Repeated dosing with 300 and 600 mg/kg for 30 days in rats resulted in no changes in body or organ weights, hematology, or blood chemistry (112). Several isolated compounds or fractions from the root have exhibited cytotoxicity in vitro, but the relevance of these findings to the whole root extract in humans is unclear (113).

In humans, valerian seems to be quite safe. In an unsuccessful suicide attempt, an 18-year-old student ingested an overdose totaling 18.8 to 23.5 g of valerian root. Thirty minutes after ingestion, the student complained of fatigue, crampy abdominal pain, chest tightness, tremor, and lightheadedness. Vital signs were normal, and the results of physical examination were notable only for mydriasis and a fine hand tremor. The patient was treated with two doses of activated charcoal, and all symptoms resolved within 24 hours (114).

There is one recent report of a possible withdrawal reaction (115). A 58-year-old man hospitalized for congestive heart failure received general anesthesia for a biopsy. After extubation, the patient developed sinus tachycardia and oliguria, tremor, signs of delirium, and high output cardiac failure. It was learned from the family that the patient had been taking valerian (530–2000 mg) five times per day for many years. Midazolam was started, and the patient improved. Although this patient was taking multiple medications, the efficacy of the benzodiazepine in resolving many of his symptoms led to the conclusion that this patient was experiencing a valerian withdrawal syndrome.

Valerian may actually antagonize the effects of alcohol; in an unusual double-blind study in human volunteers, alcohol failed to induce its predicted impairment of concentration when combined with a mixture of valepotriates from valerian (113).

VITAMINS, AMINO ACIDS, AND FISH OIL

Vitamin B_{12} and Folate

Folic acid deficiency is one of the most common nutritional deficiencies in the world and has often been associated with neuropsychiatric disorders (116). This deficiency may be an overlooked and understudied risk factor for depression. Several studies have found that up to 35% of depressed patients are folate deficient (117–120). In elderly patients, the incidence of deficiency is even more marked and may be as high as 90%. (121, 122).

Folate and vitamin B_{12} are required for the methylation of homocysteine to methionine and for the synthesis of S-adenosylmethionine. S-adenosylmethionine is involved in numerous methylation reactions involving proteins, phospholipids, DNA, and neurotransmitter metabolism. Both folate and vitamin B_{12} deficiency may cause similar neurological and psychiatric disturbances, including depression, dementia, and a demyelinating myelopathy (123, 124). Bottiglieri (116) proposes that a defect in methylation processes may be central to the biochemical basis of the psychopathology seen with these vitamin deficiencies. Folate deficiency may specifically affect central monoamine metabolism and aggravate depressive disorders. In addition, the neurotoxic effects of homocysteine may also play a role in the neurological and psychiatric disturbances associated with folate and vitamin B_{12} deficiency.

Fava et al. (125) examined the relationships between levels of folate, vitamin B_{12}, and homocysteine and response to fluoxetine (20 mg/d for 8 weeks) treatment in 213 outpatients with major depressive disorder. At baseline, depressive subtypes were assessed, a blood sample was collected from each patient, and serum metabolite levels were assayed. Response to treatment was determined by the percentage change in score on the 17-item HAM-D. Subjects with low folate levels were more likely to have melancholic depression and were significantly less likely to respond to fluoxetine. Homocysteine and B_{12} levels were not associated with depressive subtype or treatment response. The authors concluded that there was a link between low folate levels and poorer response to antidepressant treatment. They suggested that folate levels be considered in the evaluation of depressed patients who do not respond to antidepressant treatment. Although both folate (126) and methylfolate (118) have been reported to have antidepressant activity, it is unclear whether folate administration has any clinical effect in patients who are not deficient in this vitamin because there do not seem to be any studies in this population.

Adverse Effects and Interactions. Because methotrexate owes its toxicity to interfering with folate metabolism, folate may thus reduce its efficacy (127). Folate has also been reported to reduce the effectiveness of several anticonvulsants, potentially leading to seizures (128).

Tetrahydrobiopterin and SAMe

There is evidence of links among folate, tetrahydrobiopterin (an essential cofactor in the hydroxylation process in the mammalian brain), and monoamine metabolism in depression (119, 129). Tetrahydrobiopterin is necessary for the synthesis of serotonin and dopamine and has also been reported to have antidepressant activity (130). The methyl donor, SAMe, is closely linked with folate and vitamin B_{12} (cyanocobalamin) metabolism. SAMe is required in numerous transmethylation reactions involving nucleic acids, proteins, phospholipids, monoamines, and other neurotransmitters, and deficiencies of either folate or B_{12} have been found to reduce the synthesis of SAMe (and thus its levels) in the central nervous system (131).

The administration of SAMe has antidepressant properties (132–135) and, as added evidence, has been reported to induce mania in bipolar patients (136). Preliminary studies indicate that it may improve cognitive function in patients with dementia (131).

Adverse Effects and Interactions. Tetrahydrobiopterin is not commercially available. SAMe has been reported to cause mild and transient insomnia, nervousness, lack of appetite, constipation, headaches, heart palpitations, nausea, dry mouth, sweating, and dizziness (135).

Tryptophan and 5-HTP

Tryptophan, an amino acid, is a precursor of serotonin and has been used since the 1970s to increase brain levels of serotonin. Small, mostly uncontrolled studies have shown positive effects in some depressed patients (137), whereas others have not (138). The reason proposed for the equivocal effects is that tryptophan by itself may be insufficient to boost serotonin levels (139, 140). On the other hand, using tryptophan to supplement standard antidepressants has been more successful (141). Walinder et al. (142) found that 24 depressed patients started on clomipramine improved more rapidly with tryptophan supplementation. There is also considerable data suggesting that tryptophan depletion can increase depressive symptoms in patients with major depression (143) and seasonal affective disorder (144, 145). Subsequent reversal of depression with intravenous tryptophan (145) supports the notion of an antidepressant effect. Other psychiatric and neurological uses have also been described for tryptophan (146).

5-HTP is the intermediate metabolite of the amino acid L-tryptophan in the serotonin pathway. Therapeutic use of 5-HTP bypasses the conversion of tryptophan into 5-HTP by the enzyme tryptophan hydroxylase, the rate-limiting step in serotonin synthesis. Tryptophan hydroxylase can be inhibited by numerous factors, including stress, insulin resistance, vitamin B_6 deficiency, and insufficient magnesium (147). The same factors can decrease serotonin by another mechanism: By increasing the conversion of tryptophan to kynurenine via tryptophan oxygenase, less tryptophan is available for serotonin production. 5-HTP is commercially produced by extraction from the seeds of an African plant, *Griffonia simplicifolia,* and this extract is available in the United States. Antidepressant effects seem to be more consistent with 5-HTP than with tryptophan (139, 148).

Adverse Effects and Interactions. The catastrophic effects of contaminated tryptophan that caused an epidemic of EMS in 1989 (149) effectively put an end to studies in the United States. Although tryptophan is no longer marketed in the United States, it is still available in Canada.

L-tryptophan seems to interact with MAO inhibitors and with high doses of fluoxetine. More than 10 cases of behavioral or neurological toxicity have been observed after tryptophan was added to MAOIs, including phenelzine and tranylcypromine. Symptoms included hypomania, agitation, delirium, and myoclonus (150). The combination of lithium, phenelzine, and L-tryptophan has resulted in fatalities (151, 152). Five cases of toxicity have been reported with the combination of high-dose fluoxetine (50–100 mg daily) and L-tryptophan (2–4 g daily) in patients treated for OCD (153). Symptoms included worsening of OCD symptoms, agitation, insomnia, aggression, headaches, palpitations, nausea, cramping, and diarrhea. These symptoms are examples of the "serotonin syndrome" reported to occasionally occur when excessive stimulation of serotonin systems results from one serotonergic drug being added to another (154). When tryptophan is administered to patients receiving electroconvulsive therapy, seizure duration is increased, but effectiveness is not enhanced (155).

Although the same potential may exist for 5-HTP to interact with MAO inhibitors and SRIs, in many studies, they have been successfully combined to enhance the therapeutic effect (156, 157). It is unclear whether L-5-HTP is subject to the same sort of contamination as tryptophan and whether it can cause EMS. Although several cases of EMS-like syndromes have been reported in people ingesting L-5-HTP, in only one of these was the substance analyzed. In 1994, a typical case of EMS was reported in a 28-year-old woman who did not ingest the substance orally but was exposed to 5-HTP by handling powder fed to her two children (who were being treated with 5-HTP for a defect in tetrahydrobiopterin synthesis) (158). The children's father, who also prepared medication for the children,

never manifested any signs or symptoms of exposure. Although both children were asymptomatic, they were found to have increased white blood cell counts and mild eosinophilia that resolved after they were switched to a different lot of 5-HTP. Subsequent high-performance liquid chromatography analysis of the case-associated lot found a minor peak (dubbed peak X) that may represent a contaminant (examination of multiple lots revealed the presence of peak X in one of nine other lots sampled).

In 1998, peak X was reported to be a β-carboline derivative (6-hydroxy-1,2,3,4,4a,9a-hexa-hydro-β-carboline-3-carboxylic acid), similar in chemical structure to two contaminants in EMS-associated tryptophan (159). An analysis of six over-the-counter 5-HTP products purchased from health food stores (two synthetic and four seed extracts) found that all six contained low levels of peak X. Although levels of peak X were only 3% to 15% of levels found in case-implicated 5-HTP, investigators point out that consumption of 300 to 900 mg/d could bring intake to case-implicated levels. An ataxia study in which 28 patients were treated with L-5-HTP and carbidopa was halted due to the development of eosinophilia in three patients. Two of these cases demonstrated only mild elevations in eosinophils; the third patient had marked eosinophilia (36%, or 5500 eosinophils/mm^3) but had also been concurrently exposed to mace (1-chloroacetophenone).

In conclusion, contaminated L-tryptophan has been definitively associated with EMS. 5-HTP has been linked with several unusual cases of EMS-like symptoms and one convincing but unusual case of EMS in which the route of exposure was topical (and possibly respiratory) rather than oral. The recent identification of a β-carboline component in all six brands tested is nevertheless worrisome; more research needs to be done to elucidate the potential risks of 5-HTP.

Phenylalanine and Tyrosine

The amino acid catecholamine precursors phenylalanine and tyrosine have been reported to enhance mood in some individuals. There is a reasonable theoretical basis for enhancing endogenous tyrosine. Orally administered α-methyl-*para*-tyrosine induces relapse in remitted depressed patients (145), apparently by competing with endogenous tyrosine and resulting in depletion of the catecholamines dopamine and norepinephrine (145). Open trials of tyrosine (160) and phenylalanine (161) reported positive effects. However, as is often the case, improvement of trial design disadvantaged the drug. In a controlled trial of 65 patients receiving either 100 mg/kg tyrosine, imipramine, or placebo, investigators found no antidepressant effect of tyrosine (162). As with serotonin precursors, however, it is possible that combination of phenylalanine with an MAO inhibitor may enhance the therapeutic effects (163).

Adverse Effects and Interactions. There are no reports of adverse effects of phenylalanine or tyrosine. Theoretically, however, these amines could induce a sympathomimetic reaction when combined with an MAO inhibitor.

Omega-3 Fatty Acids

Neuronal membranes contain high concentrations of the essential fatty acids arachidonic acid and DHA, which are crucial components of the phospholipid bilayer (each comprises approximately 25% of the phospholipid content; see Ref. 164). It has been suggested that depletion of omega-3 PUFAs, particularly DHA, impairs membrane function and may be of etiological importance in depression, aggression, schizophrenia, and other mental and neurological disorders (165–168).

There is intriguing indirect evidence to support this in the form of reports that rapid lowering of blood lipids by hydroxymethylglutaryl coenzyme A reductase inhibitors is associated with a large number of psychiatric disorders; for example, 15% of psychiatric drug reactions were attributed to statins in a national Norwegian database (169). Reactions included aggression, nervousness, depression, anxiety, and sleeping disorders. Cholesterol-lowering therapies and low cholesterol levels have been thought to increase the risk of suicide by lowering serotonin turnover. However, drug and diet therapies to lower cholesterol also alter levels of essential fatty acids. Because levels of essential fatty acids predict 5-hydroxyindoleacetic acid levels in cerebrospinal fluid and cholesterol levels do not (170, 171), cholesterol levels may be a surrogate marker of changes in essential fatty acids.

It was recently reported that fatty acid composition of phospholipid in red blood cell membranes (thought to mirror neuronal membranes) of depressive patients showed significant depletions of total omega-3 PUFAs, particularly DHA (172). In one study, dietary supplementation with DHA and EPA showed marked mood-stabilizing activity in bipolar disorder (173). It has been theorized that adequate long-chain polyunsaturated fatty acids, particularly DHA, may reduce the development of depression just as omega-3 polyunsaturated fatty acids may reduce coronary artery disease (166).

Adverse Effects and Interactions. Some people may experience nausea, loose stools, and "fishy" breath

from high doses of fish oil. In a recent study of bipolar disorder (173), 15 patients receiving 15 g daily of fish oil containing approximately 9.6 g of omega-3 fatty acids (DHA and EPA) for 4 months had mild dose-related gastrointestinal distress as the predominant complaint.

CONCLUSION

Several herbs and dietary supplements seem to have beneficial effects on depression, anxiety, insomnia, and memory problems. More research should be conducted on these substances, many of which seem to have novel modes of action. Although most dietary supplements available in retail stores seem to be safe, they are not risk free. At the same time, case reports of adverse effects of dietary supplements, especially herbs, are often problematic. A common error is failure to differentiate among intrinsic toxicity, misidentification, contamination, and adulteration. Another problem is the failure to consider concurrent drugs (or supplements) as culprits or contributors in the reporting of adverse events. Nonetheless, caution should be used when mixing herbs or dietary supplements with drugs.

Our thanks to Steven Foster Group, Inc., for providing the color photos of the medicinal plants.

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