

## Herbs Affecting the Central Nervous System

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### LAWS AND REGULATIONS GOVERNING HERBAL MEDICINES IN THE US

As a result of the existing laws and regulations, most herbal remedies (botanicals, phytomedicines) are currently marketed in the United States as dietary supplements, a food category, not as the drugs they are. This situation stems directly from the passage, in 1962, of the Kefauver–Harris Amendments to the Federal Food, Drug, and Cosmetic Act of 1938. These amendments required drugs to be proven effective prior to marketing, in addition to the purity and safety requirements already in effect.

Although the law specifically exempted from this requirement all drugs marketed prior to 1938, which included almost all of the herbal remedies, the Food and Drug Administration (FDA), by a clever application of administrative law, i.e., regulations, circumvented the will of Congress. The agency declared that although sale could continue, any unproven claim of efficacy would cause the herb to be considered as misbranded which could result in confiscation.

To determine efficacy of over-the-counter products, in 1972 the FDA established 17 panels to evaluate, on the basis of submitted information only, the data supporting such claims. The panels were not permitted to utilize anecdotal information, product popularity, nor did they conduct detailed literature surveys. Because proof of efficacy studies are extremely expensive—current estimates for new chemical entities range up to one-half billion dollars—a limited amount of data was submitted to the panels for the old botanical remedies for which patent protection and market exclusivity with consequent profitability were doubtful.

In consequence, very few herbal remedies were approved as drugs. The few that were found acceptable included capsicum (*Capsicum* spp.) as a topical analgesic, slippery elm (*Ulmus rubra* Muhl.) as a demulcent, psyllium seed and husk (*Plantago* spp.) as a laxative, and distilled extract of witch hazel (*Hamamelis virginiana* L.) as an astringent (due to the 14% alcohol added to the final preparation). On the basis of inadequate data submission, the FDA declared peppermint (*Mentha × piperita* L.) to be an unsafe and ineffective digestive aid and placed other useful remedies such as the antitussive eucalyptus (*Eucalyptus globulus* Labill.) and the laxative prune (*Prunus domestica* L.) concentrate in the same category.

Sales of such herbal products declined for a time but began to increase once again in the 1980s as consumers became more health conscious and displayed a significant interest in natural products. Finally in 1993, Commissioner David Kessler of the FDA threatened additional controls on such products. The public rebelled, and submitting to the will of the people, Congress passed the Dietary Supplement Health and Education Act of 1994. That Act permits any herb sold in the United States prior to October 1994 to continue to be marketed as a dietary supplement (food) without FDA approval.

Labeling of such products is, however, restricted. Therapeutic claims are not permitted. This prompts the potential user to turn to the herbal literature, much of which is hyperbolic and advocacy in nature—especially on the internet—designed to promote sale of the product. Claims regarding the effect of the remedy on the structure or function of the human body are permitted on the label, but such a statement must be followed by another indicating the claim has not been approved by the FDA. A third statement must then follow indicating the product is not intended to diagnose, treat, cure, or prevent any disease. That, of course, is why the potential user wanted to purchase the product in the first place, so the entire situation becomes very confusing, even to the sophisticated consumer.

Another serious problem with the herbal product status quo is the total lack of quality standards for such preparations. Products and the companies selling them range from very bad to very good. Consumers have few resources to determine which is which, and published analyses of particular brands have been quite limited, probably due to the fear of litigation.

Other advanced nations have solved the herbal problem in one of two ways. The first is simply to allow botanicals to be sold as “traditional” drugs whose efficacy is based on long usage and anecdotal information, not on scientific or clinical studies. This is not a satisfactory solution because many of such claims of utility remain unverified.

The best solution, without question, is to modify existing regulations to allow herbal remedies to be sold as drugs, with appropriate quality standards, following absolute proof of safety and “reasonable” proof of efficacy. The reasonable qualification would allow the marketing of a product with a research investment of perhaps a few million dollars as opposed to the hundreds of millions now required. Such an expenditure is just a small fraction of the marketing budget of many herbal product manufacturers.

This type of drug approval is the one that exists today in Germany. It has functioned well there for decades, and no serious problems have been encountered. Safety and efficacy are determined by an independent panel of experts, designated Commission E, appointed by the German equivalent of our FDA. The Presidential Commission on Dietary Supplement Labels recommended the appointment of a similar panel in the United States to evaluate herbal safety and efficacy. So far, the FDA has not acted upon that recommendation nor has the agency given any indication that it will do so. Likewise, the FDA has not acted upon a long-standing petition that would allow the safety and utility of herbs to be evaluated as OTC remedies on the basis of the voluminous scientific and clinical studies already carried out in European countries, especially Germany.

Adherence to standards for drug approval designed for new synthetic chemical entities is obviously not realistic for long-used herbal remedies. In view of the fact that one-third of the adult population in this country now employs herbal remedies and the retail market approximates \$4 billion annually, serious consideration needs to be given to modifying outdated regulations. A change is urgently required to assure that consumers will be supplied with quality products providing appropriate information regarding their therapeutic utility directly on the label.

Among the numerous botanicals marketed in the United States today are several that produce significant direct or indirect effects on the central nervous system. Some of the more prominent ones have been extensively studied with respect to their chemical composition and physiological and therapeutic activities. Others continue to be employed largely on the basis of their folkloric reputations as useful remedies.

## CONSIDERATION OF SPECIFIC HERBS

### **Ephedra or Ma Huang (*Ephedra* spp.)**

Ephedra, commonly referred to by its Chinese name *ma huang*, has received much publicity recently. The herb consists of the dried green stems of several species of *Ephedra* native to Central Asia. These include *E. distachya* L., *E. equisetina* Bunge., and *E. sinica* Stapf. Ma huang has been used in China for the treatment of bronchial asthma and related conditions for more than 5000 years.

The therapeutic use of ephedra is due to its content of several closely related alkaloids of which ephedrine is both the most active and the one present in largest amount. A typical ephedra plant contains about 1.5% total alkaloids of which some 80% is ephedrine. American species of *Ephedra*, one of which is *E. nevadensis* S. Wats., often referred to as Mormon tea, contain no active alkaloids. Ephedrine was carefully researched here in the United States during the 1920s and was a standard over-the-counter (OTC) medication for many years. Like all other effective medications, it may also produce undesirable side effects.

The alkaloid's vasoconstricting effect makes it a useful nasal decongestant, but it also raises blood pressure and increases heart rate. It is an effective bronchodilator, but it also stimulates the central nervous system (CNS) with side effects ranging from nervousness to insomnia. This stimulation is greatly increased by consumption of caffeine or caffeine beverages such as coffee, tea, or cola. Consequently, ephedrine has been replaced to a large extent in over-the-counter cold and cough products by related chemicals such as pseudoephedrine or phenylpropanolamine. These have a similar action but much reduced CNS effects.

In recent years, ephedra and caffeine combination products have been promoted as appetite depressants and metabolic stimulants for weight loss, as athletic performance enhancers and, in very large doses, legal euphoriant or intoxicants. There is a considerable literature about the effects of ephedra on weight loss with some modestly favorable results. As one of my pharmacologist friends quipped, “You're bound to lose weight if you take ephedra and caffeine because you'll be so hyper the soup will slop out of the spoon before it reaches your mouth.” That is, of course, a slight exaggeration.

Detailed studies of the herb's effect on athletic performance or its euphoriant activities do not exist. But

that is of little moment because ephedra should not be taken chronically for any purpose unless the consumer is under the direct care of a competent physician. Many of the herbal products do not list the concentration of ephedrine present. Some manufacturers almost certainly “spike” their dosage forms with additional quantities of synthetic ephedrine.

As a result, the Food and Drug Administration (FDA) convened a special advisory group on ephedra in October 1995. That committee of experts made a number of recommendations regarding the sale of ephedra products, including strict dosage limitations, appropriate warning labels preventing chronic use, prohibition of sale to persons under age 18, and warnings to individuals with specific health risks.

These recommendations were never implemented, although in April 1996 the FDA did issue a warning cautioning consumers not to buy any high-dose ephedra products marketed as “legal highs.” By August 1996, the FDA had compiled a list of some 800 adverse reactions, including 22 deaths and a number of serious cardiovascular and nervous system effects, including heart attack, stroke, and seizures, which they attributed to the consumption of ephedra, often in combination with caffeine-containing herbs. (The numbers in both categories have increased significantly since that time.) Consequently, another special advisory group meeting was held, but after lengthy discussion, no consensus was reached, and no concrete recommendations were made.

Food and Drug Commissioner David A. Kessler, who attended the meeting, said the agency would consider the matter and act quickly on ephedra’s marketability, almost certainly before the end of 1996. He subsequently resigned, and no action was taken prior to the self-imposed deadline.

Finally, in June 1997, the FDA requested comment on a series of proposed restrictions on the sale of ephedra as a dietary supplement. These included a limitation of 8 mg per dose of ephedra alkaloids, labels warning consumers not to take more than 24 mg of ephedra alkaloids per day, labels advising at-risk persons not to consume ephedra, and limitation of consumption to a maximum of 7 days. As of June 1999, these proposed regulations have never been implemented.

Several states have acted, or are considering action, to control ephedra products. Most authorities continue to believe that small doses of ephedra, equivalent to not more than 40 mg of ephedrine per day, consumed on an occasional, not a chronic, basis for the relief of bronchial asthma, are safe for otherwise normal persons.

Another concern often expressed about ephedra is the possibility that the contained ephedrine may be illegally converted to methamphetamine or “speed,” a common drug of abuse, by basement chemists. Although this is possible, it is not likely because of the difficulty in separating the product from the accompanying plant material. A much more likely starting product is pseudoephedrine which is readily available in pure form. Indeed, large-scale sales of that alkaloid are now monitored by the Drug Enforcement Administration (DEA).

Ephedra remains a prime example of an age-old dilemma in medicine. Must a useful therapeutic agent be banned because of its abuse potential? In many cases, this has proven to be necessary. Whether ephedra herb falls in this category remains to be seen.

### **Ginkgo (*Ginkgo biloba* L.)**

An important breakthrough in herbal medicine took place in October 1997 when the *Journal of the American Medical Association* published the results of the first clinical trial conducted in the United States of the effect of *Ginkgo biloba* extract (GBE) on patients suffering from mild to severe dementia caused by Alzheimer’s disease or multiple clots in the blood vessels. The generally positive results showing modest improvement in the cognitive performance and social functioning of the demented patients basically confirmed results previously obtained in European studies. Some 36 clinical trials with GBE had been conducted there between 1975 and 1996.

The ginkgo tree is well-known, particularly to residents of our large cities where its resistance to pollution and its overall toughness has caused it to be much planted as an ornamental along the very busy streets. This resistance to stress has enabled the species to survive for at least 70 million years; it is often referred to as a living fossil.

The seeds of the tree, after removal of the smelly, outer fleshy layer, have been used in China, both as a medicine and a food, for thousands of years, but it is the dried green leaves, not the seeds, that yield the herbal medicine that has become so popular today. Research beginning in the 1930s identified a number of constituents in the leaves, and in 1965 a product containing 24% flavone glycosides and 6% terpenes (ginkgolides A,B,C, and bilobalide) was first marketed for the treatment of conditions resulting from cerebral and peripheral circulatory disturbances. The product subsequently became very popular as an approved drug in Germany where sales in 1996 exceeded \$163 million.

GBE is used primarily to treat cognitive deficiency, a condition caused by inadequate blood flow and nerve degeneration in the brain and expressed by symptoms such as vertigo, tinnitus, headache, short-term memory loss, reduced vigilance and concentration, and confusion. It is also useful in peripheral vascular disorders, having been shown to increase pain-free walking distance in patients with intermittent claudication. Evidence is also accumulating to support the value of GBE in alleviating sexual problems in males, particularly in those whose erectile dysfunction has been induced by the consumption of various antidepressant drugs.

Just how does GBE function to produce all of these beneficial effects? As is often the case with herbs, no single compound and no one mechanism is responsible. The ginkgo flavonoids reduce harmful brain effects by preventing the activity of enzymes that produce damaging free radicals. They also act as antioxidants scavenging any free oxygen radicals that are formed. In addition, they affect calcium transport which has a powerful influence on brain metabolism.

The sesquiterpene bilobalide reduces increased water and electrolyte levels in damaged brain tissue. The diterpene ginkgolides are potent platelet activating factor (PAF) inhibitors. PAF can contribute to brain damage not only by inducing thrombosis but also by increasing the permeability of blood vessels, allowing liquid to seep through them into brain tissue. This is likely to result in nerve damage.

In contrast to many synthetic drugs (halperidol, fluoxetine, and tacrine) for the treatment of dementia, GBE exerts its beneficial action with a much lower incidence of side effects. Only 1.67% of 10,632 patients treated with ginkgo experienced mild stomach upsets, headache, or allergic reactions in comparison to 5.42% of 2,325 patients treated with synthetic drugs who suffered these or more serious reactions.

The customary daily dose of GBE is 120–240 mg taken in 2 or 3 separate doses. A minimal 8-week course of treatment is recommended for cognitive deficiency. Contraindications to ginkgo therapy are not known, but because it does inhibit PAF, the herb should be administered cautiously in patients undergoing anticoagulant therapy utilizing either other herbs, e.g., garlic (*Allium sativum* L.), ginger (*Zingiber officinale* Roscoe), feverfew [*Tanacetum parthenium* (L.) Schultz Bip.], or synthetic drugs (warfarin).

Consumption of unprocessed ginkgo leaves in any form, including teas, should be avoided because they contain several potent allergens known as ginkgolic acids. These compounds, removed during processing of GBE, are chemically related to urushiol, the active principle in poison ivy [*Toxicodendron radicans* (L.) Ktze.]. Current regulations in Germany limit the concentration of ginkgolic acids in ginkgo preparations to a maximum of 5 parts per million. No standard has been established in the United States, but quality products do not exceed that level.

The GBE preparations long marketed worldwide are concentrated about 50-fold and contain 24% flavone glycosides and 6% terpenes, often designated 24/6. Recently, one company has made available a 27/7 product prepared by a method that increases the ginkgolide B concentration. Studies show that it produces a higher concentration of ginkgolides in the blood for a longer period of time, thus enhancing the effects of the herb.

In contrast to such improved products, it is believed that there are many substandard GBE preparations on the market today. Because of the extensive processing required, ginkgo is relatively expensive to produce, and the standard 50–60 mg tablets usually retail in the \$10–\$15 range for 60 capsules, depending on the brand. So-called bargain herbs, sometimes selling for a dollar or two for the same quantity, are very likely not bargains at all.

Sometimes one sees ginkgo advertisements touting it as a “smart pill” that improves the cognitive function of persons in the absence of any pathological condition. There is practically no evidence to show that the herb produces significant beneficial effects in the normal human brain.

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

Depression, at least in its milder forms, is a condition that seems to afflict many Americans, occasionally if not chronically. In this country, the disease is the fourth most likely reason for one to consult a family physician and costs our economy more than chronic respiratory illness, diabetes, arthritis, or hypertension. The treatment and rehabilitation expenses in the United States exceed \$12 billion annually; but the true cost, including loss of earnings, absenteeism, and loss of productivity, totals nearly \$44 billion annually.

Depression is characterized by a number of subjective complaints ranging from despondency and loss of interest to irritability and sleep and digestive disorders. One authority has noted that the depressed patient suffers from melancholia about the present, guilt about the past, and anxiety about the future. Mild to moderate depressive symptoms occur in 13–20% of the population; major depression, often characterized by suicidal tendencies, plagues 1.5–5%.

More than a dozen prescription drugs are routinely used to treat America's depression. All of them are synthetic, and they all produce more or less unpleasant side effects ranging from skin rashes to overtly violent behavior. Meanwhile, in Germany the most popular prescription drug of any type, natural or synthetic, for the treatment of depression is a concentrated extract of the flowers and leaves of St. John's wort, often simply called hypericum. More than 200,000 prescriptions per month are filled for a single brand (Jarsin) there compared to about 30,000 per month for fluoxetine (Prozac). This figure does not include sales of other hypericum products, whether prescribed or self-selected. Actually, 80–90% of the sales in Germany are prescriptions, which allows their cost to be reimbursed by the health insurance system.

During the past two years, St. John's wort has become extremely popular in the United States. In 1996, it was not even listed among the best-selling herbs. Now it is one of the five most popular botanicals. Favorable publicity on television, and subsequently in the popular press, had much to do with this phenomenal increase in use.

Many clinical trials show St. John's wort to be especially useful in treating mild to moderate depressive states. Studies in 3,250 patients found improvement or total freedom from symptoms in about 80% of the cases treated, with only 15% not responding. These results are typical of all drug therapies for depression. However, the side effects were far fewer than those observed with conventional antidepressants. The incidence was less than 2.5% and consisted mainly of gastrointestinal disturbances and allergic reactions.

The herb's multiple constituents apparently function in several different ways. Initially, St. John's wort was thought to act as a monoamine oxidase (MAO) inhibitor. This effect has now been shown to be insignificant. Some evidence supports its effect as a selective serotonin reuptake inhibitor (SSRI).

It may also inhibit COMT (catechol-*O*-methyltransferase), an enzyme capable of destroying biological amines. Still another mechanism seems to suppress interleukin-6 release, affecting mood through neurohormonal pathways. The advantage of this combined action is fewer side effects for the patient because the total response is not due to a single type of activity.

Some authorities have warned against exposure to sunlight while consuming hypericum because it may induce photosensitivity with its dermatitis and associated inflammation. However, while light-skinned animals grazing on great quantities of the herb have had such reactions, photosensitivity is very uncommon in people taking it in normal amounts. It has occurred in patients injected intravenously with very large amounts of hypericin—50 to 70 times the normal oral dose.

Although St. John's wort is marketed as a drug in Germany and has been approved there by the German equivalent of our Food and Drug Administration for the treatment of depression, anxiety, and nervous unrest, it is sold in the United States only as a dietary supplement. The most effective preparations are capsules containing an extract of the herb standardized on the basis of 0.3% hypericin. Dosage is 300–900 mg daily. Improvement of mild to moderate depression should result after 2 to 6 weeks of treatment.

### **Kava (*Piper methysticum* G. Forst.)**

The first Europeans to observe the kava plant and its ritualistic consumption by natives of Oceania were Dutch explorers Jacob Le Maire and William Schouten. In 1616, they encountered the plant in the Hoorn Islands, now a part of the French territory Wallis and Fatuna. Later travelers in the Pacific region provided a

wealth of detail regarding this highly valued and widely used pepper plant.

Long cultivated and known by a number of common names, including *kava-kava*, *ava*, *yagona*, and *yangona*, the plant is now classified by botanists as *Piper methysticum*, meaning “intoxicating pepper.” In religious and social rituals that naturally vary somewhat from island to island, the rhizome of the plant is grated (originally chewed by young people with sound teeth), mixed with water in a bowl, strained, and the resulting beverage drunk to produce a feeling of well-being.

Observers and even scientists long disagreed on the effects of kava. Captain James Cook, who observed its use during his world voyage of 1768–1771, thought the symptoms resembled those of opium. Lewis Lewin, a pioneer pharmacologist in the field of mind-altering drugs, referred to it in the 1880s as a narcotic and sedative, but noted these effects followed a period of quiet euphoria. Modern authorities call kava a psychoactive agent; it reduces anxiety much like the potent, synthetic benzodiazapines (e.g., Valium) and is a potent muscle relaxant. Kava does promote relaxation and sociability, but its effects are very different from those produced by either alcohol or synthetic tranquilizers. It does not produce a hangover, and, even more significant, it does not cause dependency or addiction.

Naturally, people were interested in finding out how kava produced these interesting effects. It was once thought that chewing the root converted its starch into sugar which then fermented to produce alcohol. Although this sounds far-fetched, *chicha*, a corn-based beer brewed by natives in Peru and Bolivia, is prepared in just this fashion. Lewin said a resinous material was the active component. Finally in the 1950s and 60s, two teams of German scientists headed by H.J. Meyer in Freiburg and R. Hänsel in Berlin found that the various activities of the kava plant were due to some 15 different chemical compounds known as pyrones. Collectively named kavapyrones or kavalactones, the compounds were found to increase the sedative action of barbiturates, to have both analgesic and local anesthetic effects, to cause muscles to relax, and to have antifungal properties.

Shortly after these findings, preparations of kava extract began to appear on the European market, usually standardized to provide a daily dosage in the range of 60–120 mg of kavapyrones. German Commission E, the group responsible for evaluating the safety and efficacy of botanical medicines, reviewed the data on kava and, in 1990, approved its use for conditions such as nervous anxiety, stress, and restlessness. It is frequently marketed as an anxiolytic. Use of kava is contraindicated during pregnancy, nursing, and in cases of depression caused by internal factors.

With an herb as potent as this one, there is naturally concern about side effects. Observations on 4,049 patients consuming 105 mg of kavapyrones daily for 7 weeks noted 61 cases (1.5%) of undesired effects. These were mostly mild and reversible gastrointestinal disturbances or allergic skin reactions. A 4-week study of 3,029 patients taking 240 mg of kavapyrones daily produced a slightly greater incidence (2.3%) of similar side effects. This would be expected because of the larger dosages used.

Long-term consumption of very large quantities of kava may result in a yellow coloration of the skin, nails, and hair, allergic skin reactions, visual and oculomotor equilibrium disturbances. For this reason, Commission E recommends that kava not be consumed for longer than 3 months without medical advice. Driving and operating machinery during consumption should be avoided.

The results of 5 controlled, double-blind clinical trials carried out with a total of 410 subjects over periods ranging from 28 to 84 days, using daily doses of kavapyrones between 30 and 210 mg, were all positive. For example, in 1995, 100 patients suffering anxiety and stress symptoms were given 210 mg of kavapyrones daily. After 8 weeks, the treated subjects were clearly improved in comparison to those receiving a placebo. As for side effects, 15 persons receiving the placebo reported them in comparison to only 5 taking kava extract.

Kava products have been steady but unspectacular sellers in Europe for several decades. Until recently, no one in the United States seemed much interested in them. Ironically, when the Food and Drug Administration began to express concern over the safety of ephedra, a stimulant herbal product, herb marketers became enthusiastic about kava, a depressant. Both herbs have psychoactive properties, but the effects are almost exactly opposite.

Kava and its contained pyrones are, without question, effective medications. They are also subject to

abuse. The kava scenario in this country is just beginning. It is too early to predict whether it will continue to be marketed freely or will eventually be subjected to rigid controls.

### **Valerian (*Valeriana officinalis* L.)**

The dried rhizome and roots of this tall perennial herb have enjoyed a considerable reputation as a minor tranquilizer and sleep aid for more than 1000 years. They contain from 0.3% to 0.7% of an unpleasant-smelling volatile oil containing bornyl acetate and the sesquiterpene derivatives valerenic acid and acetoxyvalerenic acid. Also present is 0.5% to 2% of a mixture of lipophilic iridoid principles known as valepotriates. These bicyclic monoterpenes are quite unstable and occur only in the fresh plant material or in that dried at temperatures under 40°C. In addition, various sugars, amino acids, free fatty acids, and aromatic acids have been isolated from the drug.

Identity of the active principles of valerian has been a subject of controversy for many years. Initially, the calmative effect was attributed to the volatile oil; indeed, this kind of activity was long associated with most herbs containing oils with disagreeable odors. Then, beginning in 1966 with the isolation of the valepotriates, the property was attributed to them for a 20-year period. This was done in spite of the fact that they were highly unstable and were contained in most valerian preparations only in small amounts. Finally, in 1988, it was shown that although valerian did produce CNS depression, neither the tested valepotriates, nor the sesquiterpenes valerenic acid or valeranone, nor the volatile oil itself displayed any such effect in rats. Although the active principles of valerian remain unidentified, it seems possible that a combination of volatile oil, valepotriates, and possibly certain water-soluble constituents may be involved.

Because the valepotriates possess an epoxide structure, they demonstrate alkylating activity in cell cultures. This caused concern that the herb might possess potential toxicity. However, those valepotriates decompose rapidly in the stored drug and also are not readily absorbed. For these reasons, no toxicity has ever been demonstrated in intact animals or human beings, so there is no cause for concern.

Eight clinical studies conducted between 1977 and 1996 have shown that valerian is not a suitable herb for the acute treatment of insomnia. Rather, its principal utility lies in its ability to promote natural sleep after several weeks of use, without risk of dependence or adverse health effects. Users should realize the prolonged length of time required for valerian to exert its effectiveness. When properly employed, it offers a gentle alternative to synthetic hypnotics and benzodiazapines in patients with chronic sleep disorders. Recommended dosage is 2–3 g one or more times daily.

### **Miscellaneous CNS-Depressant Herbs**

There are several botanicals with a folkloric reputation for utility in the treatment of restlessness and sleep disturbances whose efficacy is largely unproven by scientific methods. Some of them are frequently used in combination with other CNS depressants in proprietary herbal products.

*Hops*, the dried strobiles of *Humulus lupulus* L., is one of these. Although very small amounts of methylbutanol, a compound with sedative effects, have been detected in hops, clinical studies have not verified any such activity of the herb in human subjects.

*Balm or lemon balm*, the leaves of *Melissa officinalis* L., has long been purported to have sedative effects. In the only experimental study to date, its volatile oil did show some activity, but the results were not dose dependent. This suggests the effects were nonspecific.

*Passion flower*, the dried above-ground parts of *Passiflora incarnata* L., has an ancient reputation as a sleep aid. However, no controlled clinical trials have ever been conducted on single-herb preparations, so preliminary positive results in the few animal studies have not been verified.

*Lavender*, the dried flowers of *Lavandula angustifolia* Mill., yield a volatile oil, the calming and relaxing effects of which are better documented by both empirical medicine and experimental studies than the three previous herbs. Apparently, its actions are mediated by olfactory receptors, but it may possibly act directly on the CNS following systemic administration. Suitable research in human subjects is required to verify preliminary observations.

The German Commission E approved hops as a calming and sleep promoting drug, lemon balm as a sedative, passion flower for nervous restlessness, and lavender flower as a sedative. There is little or nothing in the published scientific or clinical literature to substantiate these recommendations.

This concludes a brief survey of the herbs that have either been demonstrated to have significant effects on the central nervous system or are postulated to have such effects. Because this broad overview does not present original research findings, specific references to previously established facts are not listed. They are simply too numerous to include. Instead, a general list of recommended reading in which all appropriate references may be found is presented here.

#### **RECOMMENDED READING**

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