

REVIEW

Herbal Medicines and Epilepsy: The Potential for Benefit and Adverse Effects

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The widespread availability and use of herbal medicines raise the potential for adverse effects in the epilepsy population. Herbal sedatives (kava, valerian, chamomile, passionflower) may potentiate the effects of antiepileptic medications, increasing their sedative and cognitive effects. Despite some antiseizure effects in animal models, they should not be used in place of standard seizure medications because efficacy has not been established. Anecdotal, uncontrolled observations suggest that herbal stimulants containing ephedrine (ephedra or ma huang) and caffeine (cocoa, coffee, tea, maté, guarana, cola or kola) can exacerbate seizures in people with epilepsy, especially when taken in combination. Ginkgo and ginseng may also exacerbate seizures although the evidence for this is similarly anecdotal and uncertain. St. John's wort has the potential to alter medication pharmacokinetics and the seizure threshold. The essential oils of many plants contain epileptogenic compounds. There is mixed evidence for evening primrose and borage lowering the seizure threshold. Education of both health care providers and patients is the best way to avoid unintentional and unnecessary adverse reactions to herbal medicines. © 2001 Elsevier Science

There is widespread and increasing interest in complementary and alternative medicines (CAMs), including herbal medicines (1). National surveys suggest that 42% of Americans surveyed have recently used at least one such form of therapy. People also tend to use CAM for chronic conditions that do not respond well to conventional treatments (e.g., back problems, anxiety, depression, and headaches). Further, a large proportion of CAM consumers (40%) do not disclose their use of CAMs to their physicians, and it was estimated that 15 million American adults took prescription medications concurrently with herbal medications and/or high-dose vitamins in 1997. People with epilepsy are no exception in this regard: 24% of patients in one tertiary care epilepsy clinic reported using CAMs (2). Users of CAMs were found with all levels of education, ranging from incomplete high

school education to the postgraduate level. CAM users did not significantly differ from nonusers in terms of age, gender, or race. Of the CAM users, 41% used herbal medicines and supplements. Similar to the findings of Eisenberg and colleagues (1), Peebles and colleagues (2) found that a minority (31%) of CAM users informed their physicians.

This proportion may vary across ethnic and cultural groups. A sample in Nigeria found 52% of epilepsy patients using some form of CAM (3). Further, herbs/supplements are among the most commonly used forms of CAM, and only 31% of epilepsy patients in one study informed their neurologists about their CAM use (2). This creates an enormous potential for unintentional side effects and interactions with prescription medications. Clearly it is in the best interests of health care professionals to know and understand the CAM therapies used by their patients to advise them accordingly about their safety and efficacy (4).

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TABLE 1
Sedative Herbs

Common name	Botanical name	Main active constituent
Chamomile	<i>Matricaria recutita</i> <i>Chamaemelum nobile</i>	Apigenin?
Kava	<i>Piper methysticum</i>	Kavalactones
Passionflower	<i>Passiflora coerulea</i> <i>Passiflora edulis</i>	Chrysin
Valerian	<i>Valeriana officinalis</i>	Sesquiterpenes

Note. See text for references.

Herbal medicine is an area of CAM that is readily amenable to empirical research. Although a fair amount of research is available for certain herbal medicines, much more is needed and many basic safety and efficacy issues remain to be addressed. However, active chemical constituents and mechanisms of action have been identified in several herbal medicines that are commonly sold as supplements. Numerous herbal medicines have effects in the central nervous system and on hepatic metabolism and thus have at least the theoretical potential for affecting seizures in patients with epilepsy and interacting with some antiepileptic medications. These include herbal sedatives (kava, valerian, chamomile, passionflower), stimulants (ephedra, cocoa, coffee, tea, maté, guarana, cola), cognitive enhancers (ginkgo and ginseng), and several essential oils.

This article reviews the known physiological actions of several herbal medicines and their documented effects on seizures, and suggests guidelines for physicians to use when counseling their patients with epilepsy about these products.

HERBAL SEDATIVES

Kava

Kava (*Piper methysticum*) is a plant native to the South Pacific islands, and has a historical reputation for creating relaxation (5). There is preliminary evidence that kava is effective in treating anxiety (6). The active constituents in kava appear to be the kavalactones (Table 1), including kavain, dihydrokavain, yangonin, dimethoxyyangonin, methysticin, and dihydromethysticin (5). A few mechanisms of kava have been determined, but two appear the most relevant to seizure disorders: facilitation of GABA transmission and inhibition of voltage-gated ion channels. Kavalac-

tones facilitate GABA transmission, enhancing ligand binding to the GABA_A receptor through a nonbenzodiazepine receptor site (7–9). Kavalactones also inhibit voltage-gated Na⁺ and Ca²⁺ channels at concentrations consistent with those reached in the brain by peripheral administration (10–13). It has been proposed that they bind to the Na⁺ channel in its inactivated state and prolong inactivation (12). Micromolar concentrations of kavain inhibit L-type Ca²⁺ channels, significantly reducing the subsequent release of endogenous glutamate (14).

Electrophysiological studies have shown that kavain increases slow-wave activity in both animals and humans (15, 16). Kava extract alone has minimal effects on cognitive performance in commonly used oral doses (17). However, combination with other CNS depressants such as ethanol and barbiturates produces synergistic effects (8, 17). Kavalactones have been investigated for their antiseizure effects only in animals (18–20). However, they only have a weak effect on strychnine-induced seizures (19). Kavain reduces excitatory activity in hippocampal slices, but does not appear to affect long-term potentiation or synaptic plasticity (21).

Although kava has some antiseizure effects in animal models, it has not been tested for efficacy in humans. A limited amount of kava tolerance develops with chronic treatment in mice (22). It is uncertain to what degree tolerance occurs in humans and whether a rebound hyperexcitability can occur on sudden discontinuation.

Valerian

Valerian (*Valeriana officinalis*) is a flowering herb native to Europe and Asia, but now grown in most parts of the world. The use of valerian extends back at least 1000 years, and it gained a reputation in 16th-century Europe as a treatment for epilepsy (23). Current popular interest in valerian is primarily for its effects on sleep. Preliminary research suggests that valerian may improve sleep quality (24–26).

Valerian's active chemical constituents are classified as monoterpenes and sesquiterpenes (27). Although GABA is present in valerian extracts, its brain bioavailability via oral administration is uncertain (28). However, other GABAergic mechanisms may be at work: valerian constituents inhibit enzymatic breakdown of GABA and enhance benzodiazepine binding (29, 30). Valerian has sedative effects in animals that are potentiated by barbiturates, and it reduces the anxiogenic effects of diazepam withdrawal (31–33).

Weak antiseizure effects have been shown in mice (31, 33).

In humans, valerian produces a mild decrease in attention and processing of complex information (26). There is little or no current proof that valerian has antiseizure effects. The historical reputation of valerian as a treatment for epilepsy should be considered in light of the lack of other contemporaneous treatments for epilepsy (23).

Passionflower

A few members of the passionflower family, such as *Passiflora coerulea* and *Passiflora edulis*, are known for their sedative effects. Native Americans employed a passionflower tea for its sedative and anxiolytic effects. The active constituent is believed to be the flavonoid chrysin (5,7-dihydroxyflavone), which acts as a partial agonist at benzodiazepine receptors with micromolar affinity (34, 35). Animal studies have demonstrated sedative and anxiolytic effects of chrysin (35, 36). However, it has not yet been empirically tested in humans. One study showed antiseizure effects of chrysin on pentylenetetrazol-induced seizures in mice, which were prevented by preinjection of a benzodiazepine antagonist (37).

Chamomile

German and Roman chamomile (*Matricaria recutita* and *Chamaemelum nobile*, respectively) are perennial flowering herbs that grow in widespread regions, including Europe, Africa, and Asia. It has been known traditionally for its mild relaxing effects. A candidate constituent for this effect is apigenin, a flavonoid chemical that binds specifically with micromolar affinity to the benzodiazepine receptor (38). However, the sedative effects are not blocked by a specific benzodiazepine antagonist (Ro 15-1788), so its mechanism is still uncertain (39). Apigenin does have anxiolytic and sedative effects in some animal models, but no antiseizure effects. Although it is listed as Generally Regarded as Safe (GRAS) by the Food and Drug Administration, evidence for its effectiveness in humans has yet to be demonstrated empirically.

HERBAL STIMULANTS

There are several herbal supplements with known stimulant effects that may exacerbate seizure disor-

TABLE 2
Stimulant Herbs

Common name	Botanical name	Main active constituent
Ephedra	<i>Ephedra</i> species	Ephedrine
Cocoa	<i>Theobroma cacao</i>	Caffeine, Theophylline, Theobromine
Coffee	<i>Coffea arabica</i>	Caffeine, Theophylline, Theobromine
	<i>Coffea robusta</i>	
Cola, kola	<i>Cola acuminata</i>	Caffeine, Theophylline, Theobromine
	<i>Cola nitida</i>	
Guarana	<i>Paulinia cupana</i>	Caffeine, Theophylline, Theobromine
Maté	<i>Ilex paraguariensis</i>	Caffeine, Theophylline, Theobromine
Tea	<i>Camellia sinensis</i>	Caffeine, Theophylline, Theobromine

Note. See text for references.

ders. The most common herbal stimulants contain the drugs ephedrine and caffeine (Table 2).

Ephedra

The stimulant drug ephedrine is present in many species of *ephedra* (e.g., *Ephedra sinica*), which are often referred to by the Chinese name *ma huang*. Ephedra has been used traditionally as a stimulant and a treatment for asthma. *Ephedra sinica* contains approximately 1.25% ephedrine, as well as several other related alkaloids such as pseudoephedrine, methylephedrine, and norpseudoephedrine (40). The stimulant and sympathomimetic effects of ephedrine are mediated by its agonist effects at α_1 , β_1 , and β_2 receptors (41).

An analysis of adverse events reported by physicians to the FDA between June 1, 1997, and March 31, 1999 (42), revealed several cases of seizures temporally associated with ephedra ingestion. No apparent prior history of seizures was reported for these cases, but the ephedra was taken in combination with other stimulants (e.g., caffeine or phenylpropanolamine hydrochloride). This is a small number of seizures relative to the large numbers of people who consume ephedra in the general population. It is also small relative to the overall number of reported adverse events (7/140), but it underscores the potential danger to those at risk for seizures. Other monoamine stimulants, amphetamine and cocaine, can similarly exacerbate seizure disorders (43, 44).

Caffeine-Containing Stimulants

Caffeine is one of the most consumed stimulants in the world. Along with its methylxanthine relatives, theophylline and theobromine, it is present in eight species of plants that are commonly available as food and supplements. These include coffee (*Coffea arabica* and *Coffea robusta*), tea (*Camellia sinensis*), cocoa (*Theobroma cacao*), cola or kola (*Cola acuminata* and *Cola nitida*), maté (*Ilex paraguariensis*), and guarana (*Paulinia cupana*). Coffee, tea, and cocoa are arguably the most popular in Western countries, but other caffeine-containing herbs are still readily available, often in supplement form. While coffee, tea, and cocoa are widely known to contain caffeine, its presence in the remaining plants is not as well known to consumers, raising the likelihood of unintentional caffeine ingestion. Further, many supplements are available that include combinations of herbs containing caffeine and/or other stimulants, such as ephedrine, creating the possibility for additive or synergistic effects (45).

At normally consumed doses, caffeine is believed to mediate its stimulant effects through inhibition of adenosine receptors (46). Antagonism of presynaptic adenosine receptors causes a disinhibitory release of a variety of neurotransmitters, with a net excitatory effect. Caffeine and theophylline have pro-seizure effects in rats given kainic acid or Metrazol, facilitating chemically and electrically induced epileptiform activity in the CA3 region of hippocampal slices (47). Caffeine increases the amplitude of the basal field potentials from electrical stimulation of CA1 pyramidal neurons in hippocampal slices (48). Conversely, adenosine agonists reduce chemically induced epileptiform discharges, which is reversed by caffeine (49). Caffeine lengthens afterdischarges in kindled amygdaloid seizures (50). Caffeine is also used to prolong seizures induced by electroconvulsive therapy in patients with depression (51).

HERBAL COGNITIVE ENHANCERS

Ginkgo

A few herbal medicines have gained a reputation for enhancing cognitive functions, particularly memory. Ginkgo is a seed-bearing tree that has characteristic fan-shaped leaves, and has a traditional reputation for improving cognition. It is perhaps the most common herb with reputed cognitive effects, and has been the subject of a fair amount of research. Research supports modest cognitive effects in patients with de-

TABLE 3

Cognitive Enhancer Herbs

Common name	Botanical name	Main active constituent
Ginkgo	<i>Ginkgo biloba</i>	Flavonoid glycosides, terpene lactones
Ginseng	<i>Panax ginseng</i> <i>Panax quinquefolium</i>	Ginsenosides

Note. See text for references.

mentia, and preliminary support exists for effects in normal subjects (52–55). The active constituents in ginkgo are believed to be flavonoid glycosides and terpene lactones (Table 3). A definitive mechanism of action for the promnestic effects of ginkgo has not been identified; ginkgo is known to enhance cholinergic transmission (56–58). Some ginkgo constituents, namely bilobalide, may have neuroprotective and antiseizure effects (59, 60). However these effects must be considered in the context of the total effects of total ginkgo extract, which is how it is most commonly consumed.

The U.S. Food and Drug Administration's Special Nutritionals Adverse Event Monitoring System (SN/AEMS) currently lists seven cases of seizures in people taking ginkgo reported by physicians (61). The preparations were all from different manufacturers, and while four involved multi-ingredient preparations, three contained only ginkgo extract. It cannot be determined whether ginkgo was causal to these cases; the database does not give details regarding dosage, any history of seizures, or whether they were worsened by taking ginkgo. This incidence of reported seizures is very small in comparison to the large numbers of people consuming ginkgo in the normal population. One case has been reported of generalized convulsions after a large dose of ginkgo nuts (62). One electrophysiological study showed that ginkgo extract causes increases in alpha and decreases in delta and theta activity in humans (63).

Ginseng

Ginseng typically refers to two species of plants, Asian and American ginseng (*Panax ginseng* and *Panax quinquefolius*, respectively). It has a long history of use across several cultures to treat a variety of ailments, including memory loss. Much research has been published on the promnestic effects of ginseng in animal studies, but evidence for such effects in humans is

lacking (64). The major active constituents in ginseng are a class of chemicals called the ginsenosides (65). Several mechanisms are possible for ginseng's putative cognitive effects, but ginseng is also known to activate the hypothalamo-pituitary-adrenal axis. Ginsenosides elevate plasma ACTH and corticosteroids, and ginsenoside Rg1 is a functional ligand at the glucocorticoid receptor (66–68). Since corticosteroids have excitatory and pro-seizure effects, ginseng may best be avoided by those with seizure disorders (69–71).

ST. JOHN'S WORT

St. John's wort (*Hypericum perforatum*) is an herbal medicine with a historical reputation for treating depression. There is some empirical evidence for this effect. Meta-analyses have suggested that St. John's wort is superior to placebo for treatment of depression of mild to moderate severity (72–74). However, one recent study has challenged these large-scale analyses (75). St. John's wort has been shown to be equivalent to some pharmaceutical antidepressants, including fluoxetine and sertraline (76–79). The putative antidepressant effect of St. John's wort may be mediated by increasing monoamine activity through a variety of mechanisms (80–82). However, it also has effects on GABAergic and glutamatergic systems (82, 83).

St. John's wort may interact pharmacokinetically with antiepileptic medications. The chemical constituent hyperforin alters drug metabolism by activation of the pregnane X receptor (84). This, in turn, alters expression of cytochrome P450 (CYP) 3A4 monooxygenase, inducing the enzyme. This has been shown to cause pharmacokinetic interactions with the drugs warfarin, digoxin, theophylline, cyclosporin, and indinavir, potentially leading to decreased efficacy (85–89). Induction of CYP 3A4 by St. John's wort raises the potential for interactions with phenytoin, carbamazepine, and phenobarbital. However, it does not alter clearance of carbamazepine (90). Potential interactions with phenytoin or phenobarbital have not been empirically tested.

HERBAL ESSENTIAL OILS

Burkhard and colleagues (91) have reported the epileptogenic potential of the essential oils of several plants (Table 4). They present cases of three individuals with no risk factors or prior history of seizures

TABLE 4
Herbal Essential Oils

Common name	Botanical name	Epileptogenic compound
Eucalyptus	<i>Eucalyptus globulus</i>	Cineole
Fennel	<i>Foeniculum vulgare</i>	Fenchone
Hyssop	<i>Hyssopus officinalis</i>	Pinocamphone, cineole
Pennyroyal	<i>Mentha pulegium</i> or <i>Hedeoma pulegioides</i>	Pulegone
Rosemary	<i>Rosmarinus officinalis</i>	Cineole, camphor
Sage	<i>Salvia officinalis</i>	Thujone, camphor, cineole
Savin	<i>Juniperus sabina</i>	Sabinylacetate, camphor, thujone
Tansy	<i>Tanacetum vulgare</i>	Thujone, camphor, cineole
Thuja	<i>Thuja occidentalis</i>	Thujone, fenchone, cineole
Turpentine	<i>Pinus</i> species	Pinenes?
Wormwood	<i>Artemisia absinthium</i>	Thujone

Source: Burkhard PR, Burkhardt K, Haenggeli CA, Landis T. Plant-induced seizures: reappearance of an old problem. *J Neurol* 1999;246:667–70.

who experienced generalized tonic-clonic seizures after using essential oils orally and transdermally. After discontinuation, they returned to their premorbid seizure-free status.

Plant-derived essential oils with epileptogenic effects include eucalyptus (*Eucalyptus globulus*), fennel (*Foeniculum vulgare*), hyssop (*Hyssopus officinalis*), pennyroyal (*Mentha pulegium* or *Hedeoma pulegioides*), rosemary (*Rosmarinus officinalis*), sage (*Salvia officinalis*), savin (*Juniperus sabina*), tansy (*Tanacetum vulgare*), thuja (*Thuja occidentalis*), turpentine (*Pinus* species), and wormwood (*Artemisia absinthium*). Many of these plants are commonly used as culinary spices and may seem innocuous at face value. However, as essential oils they contain concentrated amounts of compounds with established epileptogenic effects. Essential oils are sold over-the-counter, and the epileptogenic effects of certain ones are not widely known.

OTHER HERBAL MEDICINES: EVENING PRIMROSE AND BORAGE

Evening primrose (*Oenothera biennis*) has become popular as a treatment for premenstrual syndrome, although experimental results have been conflicting (97). Borage (*Borago officinalis*) has a reputation for treating depression, inflammation, fevers, and coughs, although these uses have not been empirically tested. Both evening primrose and borage are sources of the

omega-6 fatty acid γ -linolenic acid (GLA) (93). GLA reportedly lowers the seizure threshold (93), although some studies report antiseizure effects of fatty acids (94, 95).

IMPLICATIONS FOR PATIENTS WITH EPILEPSY

Sedative herbs such as kava and valerian may potentiate the effects of antiepileptic medications, intensifying side effects such as lethargy and cognitive impairments. Passionflower and chamomile may also have similar sedative effects in humans, although they have not been tested in humans in this regard. Kava, valerian, and passionflower have shown some antiseizure effects in animal models, but they have not been tested in humans and should not be used in place of pharmaceutical antiepileptic medications. Patients should also be advised against discontinuation of antiepileptic medications in favor of herbal remedies, since rebound seizures may occur on withdrawal of seizure medications.

Stimulant herbal medicines such as ephedra, coffee, tea, cocoa, maté, cola, and guarana may exacerbate seizures by lowering the seizure threshold or prolonging the duration of seizures. The ubiquity of caffeine in herbal, over-the-counter preparations, and soft drink beverages may make it seem innocuous. Maté, cola, and guarana are more recent additions to the West, and many people are unaware that they contain caffeine. Further, many over-the-counter preparations employ combinations of these drugs, creating the likelihood of additive or synergistic effects.

Potential cognitive enhancing herbal medicines such as ginkgo and ginseng may work through a variety of neurochemical mechanisms and also may exacerbate seizures under some conditions. Ginseng is known to elevate plasma levels of corticosteroid hormones, which can aggravate seizures.

St. John's wort may alter the pharmacokinetics of some antiepileptic medications, but does not seem to affect carbamazepine. It may alter the seizure threshold, as do pharmaceutical antidepressants, but the directionality and magnitude of this are uncertain. Pharmaceutical antidepressant drugs are known to lower the seizure threshold, increasing the risk for seizures (96). However the magnitude of this risk varies with the specific antidepressant. For example, the selective serotonin reuptake inhibitors (SSRIs) exhibit low risk and may be well tolerated. To the extent that St. John's wort interacts with monoamine, GABAergic,

and glutamatergic transmission, it may alter the seizure threshold. However, this has yet to be empirically demonstrated.

Numerous essential oils are available that contain concentrations of known epileptogenic compounds. Many of the plants from which these oils are derived are commonly used in cooking, which may obscure the potent nature of the essential oils. Evening primrose and borage have been cited to potentially lower the seizure threshold, but research in this regard is mixed and so no certain conclusions can be drawn. These herbal preparations may best be avoided until this issue is clarified.

CONCLUSIONS

Available evidence suggests that many herbal medicines may have the potential for adverse effects in people with seizure disorders. A combination of factors can compound this issue, including the popularity and widespread use of herbal medicines by laypersons, the reluctance of many patients to discuss their use of herbal medicines with their physicians, and a lack of knowledge about the safety and efficacy of many herbal medicines among both patients and health care providers.

Many herbal medicines are sold over-the-counter as dietary supplements, as long as they do not advertise specific claims about treatment of a disease or condition, such as obesity (97). They must have a basic level of safety for the Food and Drug Administration to allow their sale. However, an herbal medicine that may be relatively safe in the general population may also interact adversely with the symptomatic expression of medical conditions, such as epilepsy, and their treatments. Arguably, the same potential risk exists for pharmaceutical over-the-counter medications. Thus, both patients and health care providers must educate themselves on the contraindications of herbal medicines, as well as pharmaceutical medications, to avoid improper use or harmful effects. Further research is needed to establish the safety and efficacy of many herbal medicines in patients with epilepsy.

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