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Herbs in Epilepsy: Evidence for Efficacy, Toxicity, and Interactions

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Herbs and dietary supplements enjoy widespread use in the treatment of epilepsy although supportive data yielding efficacy and safety are lacking. Ten specific products, American hellebore, betony, blue cohosh, kava, mistletoe, mugwort, pipsissiwa, skullcap, valerian, and melatonin, have either multiple-cited recommendations for use in epilepsy or a rationale for antiepileptic action and are discussed in detail. These items paradoxically often have a proconvulsant effect in addition to potentially serious adverse effects. Herb-drug interactions also occur at the level of the P450 hepatic enzyme system of drug catabolism and the P-glycoprotein transport system regulating the entry of exogenous compounds into the vasculature or blood-brain barrier. Thus, significant pharmacokinetic interactions may occur, in addition to pharmacodynamic interactions and proconvulsant effects of alternative medications themselves. Patients should be inquired as to the nature of any alternative medicine products they are using, with the view that these products may be reasonable if traditional antiepileptic drug therapy is continued, potential adverse effects of the alternative agents are monitored, and the alternative and traditional agents do not conflict.
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Complementary and alternative medications continue to offer therapeutic approaches to patients with neurologic disorders, including epilepsy. Although there is a relative dearth of evidence-based data and a lack of a regulatory environment, market share information indicates that 20% of the adult population uses herbal products.[1,2] An additional problem of 2-way denial is present wherein patients will underreport use of alternatives, whereas physicians may discount their significance.[3] Risks, however, include a range of adverse effects, inadvertent proconvulsive properties, and herb-drug interactions. The latter invoke effects on metabolism of standard antiepileptic drugs (AEDs) and factors related to medication absorption from the gastrointestinal tract and transport across the blood-brain barrier.

There are several ways of classifying alternative therapy globally including excellent efficacy and tolerability (eg, pyridoxine dependent epilepsy), excellent efficacy but poor tolerability (eg, adrenocorticotrophic hormone in infantile spasms), promising but unproven efficacy (eg, intravenous immunoglobulin in Landau-Kleffner syndrome), and unproven efficacy with little evidence of toxicity (eg, herbals, vitamin supplementation, and acupuncture). One may add, however, a category of deleterious effects based on proconvulsant effects and interactions with standard therapies. It is rational to consider alternative medicine acceptable in medical practice if the patient continues with traditional therapies and the alternative therapies and traditional therapies do not conflict. We do believe, however, that evidence-based medicine should apply, and alternative medicine use should depend on evidence for efficacy with an acceptable safety profile. Traditional therapy should not be abrogated on behalf of alternative medicines.

Commonly Used Herbs

The top selling herbs in the United States include ginkgo, St John's wort, ginseng, garlic, echinacea, saw palmetto, kava, Pycnogenol (Horphag Research, Geneva, Switzerland), cranberry, valerian root, evening primrose, bilberry, and milk thistle[4] (Table 1). The total in annual US sales amounts to nearly $690 million, with the top 13 herbs accounting for over 90% of that amount. We identified herbs described as effective or possibly effective for the treatment of seizures in at least 2 widely available and recognized reference texts.[4,5]

American Hellebore

American hellebore (*Veratrum viride*) has been used for diverse indications, including neuralgia, peritonitis, pneumonia, and seizures. Synonyms for American hellebore are false

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Table 1 Top-selling Herbs in the United States[4]

Herb	Reported Common Uses	Annual Retail US Sales ($ Millions)
Ginkgo	Dementia Circulatory Vertigo	150.9
St John's Wort	Depression	140.4
Ginseng	Enhancement of mental and physical capacities	95.9
Garlic	Circulatory (increases blood pressure) Hyperlipidemia	84.0
Echinacea/ goldenseal	Immune stimulant Antioxidant/anti-inflammatory (used for upper respiratory infection/influenza)	69.7
Saw palmetto	Benign prostatic hypertrophy Chronic cystitis	32.1
Kava	Anxiolytic Analgesic Antiepileptic	16.6
Pycnogenol/ grape seed	Antioxidant Anti-inflammatory	12.1
Cranberry	Urinary tract infection Kidney stones	10.4
Valerian root	Mild Sedative (anxiety, insomnia)	8.6
Evening primrose	Cardiovascular disease (elevated cholesterol) Rheumatoid arthritis Cough, bronchitis Multiple sclerosis Eczema Premenstrual syndrome	8.5
Bilberry	Diarrhea Cataracts, glaucoma Diabetes mellitus	6.4
Milk thistle	Liver function	4.9

hellebore, green hellebore, Indian poke, itchweed, and swamp hellebore. The common trade name is cryptenamine. The plant is found in the United States. It contains ester alkaloids that are chemically similar to steroids. American hellebore has variable cardiovascular effects. High doses have been found to elevate blood pressure, but other resources suggest its use to lower blood pressure, heart rate, and respiratory rate. The plant causes cardiac tissue, nerve membranes, and muscle tissue to become more highly depolarized, leading to increased muscle tone. This is a highly toxic drug with a low therapeutic index.

Adverse effects on the central nervous system (CNS), heart, gastrointestinal (GI) system, lungs, and autonomic nervous system have been reported in patients using American hellebore. Paresthesiae, extraocular muscle paralysis, hypertonia, weakness, and seizures may occur with CNS toxicity. Cardiac effects include syncope and bradyarrhythmias. GI symptoms include abdominal pain and distention, nausea, and vomiting. Respiratory symptoms are dyspnea and respiratory depression. Autonomic effects are increased salivation and either hypertension or hypotension.

Pregnant women should avoid American hellebore because ingestion of the plant is associated with serious teratogenicity, including cyclopia and other facial deformities in animal studies. American hellebore is not recommended for medicinal use, particularly during pregnancy.

Betony

Folklore suggests many indications for the use of betony (*Stachys officinalis*), including anxiety, asthma, bronchitis, diarrhea, headache, heartburn, palpitations, renal disease, roundworm, seizures, stomach aches, toothaches, and wounds. During the Middle Ages, it was regarded for its "magical powers" and used as a panacea for a wide range of diseases. It is traditionally used as a tea although some herbalists advocate smoking betony for the treatment of headache. Despite multiple claims, there is little available evidence to support the use of betony for any therapeutic application. Synonyms for betony are bishopswort and wood betony. Common trade names are Herb-a-Calm Formula, Herbagessic Formula, and HerbVal Formula (Viable Herbal Solutions, Langhorne, PA). Betony is a member of the mint family indigenous to Europe, northern Africa, and Siberia. The actions of betony are thought to come from tannins, which constitute 15% of betony. Reported side effects include GI irritation (diarrhea, nausea, and anorexia), hypotension, and hepatic dysfunction. Uterine contractions have also been reported; pregnant women should not use betony.

Blue Cohosh

Blue cohosh (*Caulophyllum thalictroides*) has been touted for the properties of seizure reduction as well as the augmentation of menstrual flow and labor. The latter has led to reported use in midwifery. The active agent, methylcytosine, has similarities to nicotine. Synonyms for blue cohosh are blue ginseng, *Caulophyllum*, papoose toot, squawroot, and yellow ginseng. Common trade names are Blue Cohosh Low Alcohol (Nature's Answer, Hauppage, NY), Blue Cohosh Root (Starwest Botanicals, Rancho Cordova, CA), and variants thereof. This plant is a perennial found in the Midwestern and Eastern United States and Canada. As suggested by the name, its seeds are bright blue. Actions in animal studies include the stimulation of smooth muscle in coronary vessels, the small intestine, and the uterus. Antifertility, anti-inflammatory, and antimicrobial actions have been reported.

Adverse reactions include chest pain, hypertension, abdominal cramps, diarrhea, hyperglycemia, and poisoning in children after the ingestion of seeds. Children are often attracted to their bright blue color. Blue cohosh is contraindicated in pregnancy because of increased uterine contractions and teratogenesis. At least 2 cases of severe neonatal heart failure were linked to consumption during pregnancy. People with angina and other cardiac symptoms should not use blue cohosh.

Kava

Kava (*Piper methysticum*) is commonly used as a ceremonial beverage in the South Pacific, but its use has spread as a widely used anxiolytic. Limited studies have suggested several mechanisms of potential neuromodulatory effects. Kava is a strong L-type Ca^{+2} channel inhibitor and weak Na^{+} channel blocker. Kava increases early K^{+} outward current and gamma-aminobutyric acid transmission. A serotonin 1A agonist effect has been described.[6] A meta-analysis of 7 double-blind, randomized, placebo-controlled trials found some superiority over placebo for the treatment of anxiety but statistical significance in only 3.[7] One relatively large study of 101 patients with anxiety showed improvement ($P < .0001$) on the Hamilton Anxiety Scale but not on the Clinical Global Impression Scale.[8] Case reports suggest usefulness in "spinal seizures," epilepsy, and psychosis. Anecdotal reports claim positive results for its use to treat asthma, depression, insomnia, muscle spasms, pain, rheumatism, sexually transmitted disease, and wound healing.

Synonyms for kava are Ava, Awa, kava-kava, kawa, Kew sakau, Tonga, and yagona. Common trade names are Aigin (Hevert-Arzneimittel, Nussbaum, Germany), Antares (Krewel Meuselbach, North Rhine-Westphalia, Germany), Ardeydystin (Ardeypharm, North Rhine-Westphalia, Germany), Kava Kava Liquid (NOW Foods, Bloomingdale, IL), Kavatrol (Natrol, Chatsworth, CA), Laitan (Altana Pharma, Wesel, Germany), Nervonocton N (A. Pfluger Homoopathisches Laboratorium, Rheda-Wiedenbrück, Germany). *P methysticum* is a member of the black pepper family indigenous to the South Pacific islands. Clinical effects are said to include anesthetic activity, muscle relaxation, mild euphoria, and pupillary dilatation. It is also said to have fungistatic properties.

Hyporeflexia, sedation, ataxia, headache, dizziness, vision changes, hypertension, diarrhea, thrombocytopenia, lymphopenia, weight loss, dyspnea, skin hypersensitivity, dopamine antagonism, conjunctival injection, and hematuria have been reported by its users. The German government has investigated whether kava should be more closely regulated after reports of hepatotoxicity in Germany and Switzerland.[9] Kava should be avoided in pregnant and lactating women; children under 12; and patients with renal disease, neutropenia, and thrombocytopenia.

Mistletoe

Mistletoe (*Viscum* sp) has widespread use as a remedy for various ailments, even though it has known toxic effects. In mice, mistletoe protects against pentylenetrazole-induced and bicuculline-induced seizures. No change was seen in the N-methyl-D-aspartate (tonic) seizure model.[10] Mistletoe has been anecdotally used to treat arteriosclerosis, cancer, depression, epilepsy, hypertension, headaches, insomnia, nervousness, sterility, tachycardia, tensions, ulcers, and urinary disorders. There have been anecdotal reports suggesting antineoplastic effects although a recent meta-analysis indicated that there is weak evidence at best to suggest any role in improvement of survival or quality of life in cancer patients.[11] Alternative names for mistletoe are all-heal, birdlime, devil's Fuge, European mistletoe, golden bough, and *Viscum*. Common trade names are helixor, iscador, Iscucin, Plenosol, and *Viscum album* Quercus-Frischaft. *Viscum* plants (leaves, branches, and berries) are native to England, Europe, and Asia. North American mistletoes are primarily used as Christmas greens. They are parasitic plants that grow on fruit trees, poplars, and oaks. A number of components in mistletoe may have adverse effects, including amines, acetylcholine, choline, histamine, tyramine, flavonoids, lectins, alkaloids, and acids.

Patients using mistletoe have reported side effects, including coma, sedation, seizures, bradycardia, cardiac arrest, cardiac depression, hypotension, hypertension, hepatitis, uterine stimulation, nausea, vomiting, diarrhea, gastritis, psychosis, miosis, and mydriasis. Mistletoe should not be used in pregnant or lactating women. Dehydration and electrolyte imbalance should be closely monitored in patients using mistletoe.

Mugwort

Mugwort (*Artemisia vulgaris*) has been used to correct breech presentation.[12] The lack of clinical data supporting mugwort's safety and efficacy, however, warrants careful review of its use. Synonyms for mugwort are ai ye, armoise commune, artemesia, carline thistle, felon herb, gemeiner Beifuβ, hierba de San Juan, sailor's tobacco, St John's plant (not to be confused with St John's wort), Summitates artemisiae, and wild wormwood. The common trade name is Phyto-Surge (PhytoPharmica, Green Bay, Wisconsin).

The plant is a member of the daisy family and is native to northern Europe, Asia, and North America. Mugwort has been used for multiple clinical scenarios besides seizures (eg, as an abortifacient, analgesic, antihelminthic, antibacterial, antiflatulent, antifungal, antirheumatic, antiseptic, aphrodisiac, appetite stimulant, bile stimulant, CNS depressant, diaphoretic, digestive, diuretic, emetic, expectorant, hemostatic, laxative, sedative, uterine stimulant, and uterine vasodilator). Mugwort is used in moxibustion treatments at acupuncture points in Chinese traditional medicine.

Reported side effects include the stimulation of uterine contractility, contact dermatitis, and anaphylaxis. Pregnant women as well as lactating mothers should avoid mugwort, as should patients with coagulopathies and gastroesophageal reflux. Mugwort pollen is an allergen that contributes to hay fever, with cross-sensitivity to hazelnut, tobacco, honey, or jelly.

Pipsissewa

Pipsissewa (*Chimaphila umbellate*) is marketed for anticonvulsant, antispasmodic, and diuretic effects. Safe doses and therapeutic claims have not been evaluated in clinical studies. Synonyms are ground holly, prince's pine, spotted wintergreen, and wintergreen. The common trade name is pipsissewa Fresh Upper Leaves (Herb Pharm, Williams, Oregon). The plant is a creeping perennial herb native to Eurasia and northern North America. Hypoglycemic action in animals has been reported, as has stimulation of renal tubular function. Reported side effects include nausea, vomiting, diarrhea, and rash. Patients with GI disorders, iron deficiency, and

malabsorptive disorders should exercise caution when using pipsissewa. It should not be used in lactating patients.

Scullcap

There is little clinical research regarding the use of scullcap (*Scutellaria laterifolia* and *S baicalensis*), and insufficient evidence recommends it for any condition or disease. Limited trials evaluating immunogenic[13] and hematopoietic benefits[14] in cancer patients have suggested possible benefits. Anti-inflammatory action is reportedly produced by inhibiting interleukin-1, prostaglandin E_2, and leukotriene B4.[15] Other studies show decreased 5-fluorouracil and cyclophosphamide myelotoxicity and tumor cell viability in mice.[16] In vitro studies have evaluated its effect as an antiviral agent (influenza, HIV, and Epstein-Barr virus). It may have antioxidant effects.[17] Synonyms for scullcap are helmet flower and hoodwort. The source is leaves and roots of *S laterifolia* and *S baicalensis*, which are native to temperate regions of North America. Scullcap is marketed as an anticonvulsant, sedative, antihelminthic, and antibacterial and is also said to have anti-inflammatory, cholesterol-lowering, and antisplasticity effects.

The use of scullcap may result in hepatotoxicity, confusion, seizures, stupor, cardiac arrhythmias, and fasciculations. Liver function studies should be monitored while using skullcap. Pregnant and lactating mothers should avoid scullcap. Commercial forms are often adulterated with other herbs and alcohol.

Valerian

Valerian (*Valeriana officinalis*) is a commonly used sleep aid. Synonyms for valerian are all-heal, Baldrian, cat's love, and wild valerian. Historically, it has been used to treat digestive and upper respiratory symptoms.[18] Valerian has been used as an antiepileptic for centuries and at times was considered a first-line treatment for epilepsy. The chemical composition of valerian varies greatly depending where it is grown and age because decomposition occurs with time. Up to 1% of the root may be converted to isovalerate, which is structurally similar to valpropate. Valerian itself may not be well tolerated, with side effects including drowsiness and an unpleasant taste and odor analogous to sweaty socks. Clinical trials have been initiated for isovaleramide, and dosages up to 2,400 mg/d appear to be well tolerated.[19] The amount of isovalerate being evaluated, however, is approximately 20 times higher than would be available in a single dose of valerian. Valerian has a historic record of importance in epilepsy, but there is no confirmatory evidence of antiseizure effects.[20]

Melatonin

Melatonin is marketed as a dietary supplement, and its widespread use warrants discussion. Melatonin is a chronobiotic, a term analogous to nutribiotic, which is applied to vitamins and herbs. Melatonin is a derivative of serotonin metabolism and is normally produced by the pineal gland and secreted to the hypothalamus where it promotes sleep. Melatonin levels are regulated by circadian rhythm, with peak levels occurring around 2 to 3 AM, followed by a rapid fall at approximately 6 AM. Supplemental melatonin can alleviate jet lag and disorders of delayed sleep phase. A normal sleep phase can be restored in patients with delayed sleep phase syndrome after the administration of melatonin for 2 to 6 weeks.

Some have reported an antiseizure effect of melatonin, and animal models suggest a link between seizures and melatonin. In animals, antimelatonin antibody can induce seizures.[21] Removing the pineal gland, where melatonin is made, produces seizures in rats.[22] Audiogenic seizures in rats produce pineal damage.[23] No change in melatonin rhythms were observed in patients after daytime tonic-clonic, complex partial, or psychogenic seizures.[24] Low melatonin levels have been observed in children with photosensitive epilepsy.[25] An increase[26] and a decrease[27,28] in seizure frequency have been observed in epilepsy patients using supplemental melatonin. Melatonin's use as a sleep aid may confound the assessment of improved seizures associated using melatonin.

Melatonin is available as immediate-release capsules (containing lactose and starch), slow-release capsules (psyllium), slow release (Osmotic-controlled Release Oral Delivery System), and a transdermal patch. It is recommended to use synthetic (crystalline/white, not beef-derived [yellow/brown]) to avoid allergic reactions such as serum sickness. Clinical dosing varies greatly, but doses range from 0.1 to 2,000 mg/d in anecdotal reports. A usual recommended dose is generally in the range of 2 to 5 mg, but little evidence supports this other than common usage. The oral bioavailability of melatonin is 10% to 15% absorption, and metabolism is via the cytochrome P450 (1A2 enzyme) system of the liver. Melatonin crosses the blood-brain barrier rapidly; the elimination half-life is 30 to 50 minutes. Melatonin has been shown to interact with AEDs. An acute oral dose of valproic acid suppressed nocturnal melatonin,[29] and carbamazepine may decrease melatonin levels.[30]

Melatonin affects multiple systems, including circadian rhythms, reproductive organs, thermoregulation, and immunoregulation.[31] A recent meta-analysis of 9 randomized controlled trials with over 425 subjects showed no evidence of adverse effects with use limited to 3 months.[32] In a study of 23 children with intractable epilepsy, 10% reported minor adverse effects, specifically headache, rash, and abdominal pain, which did not mandate cessation of the drug.[28] Concerns have been expressed regarding vasoconstriction and effects on puberty based on animal studies,[33] and the effects of chronic melatonin use are unknown.[34]

Important Herb-Drug Interactions

Both underreporting of herbal and supplement products by patients and the lack of recognition of potential herb-drug interactions by physicians represent important issues in clinical practice. There are 3 major types of interactions involving herbs and epilepsy: pharmacokinetic effects, the effects of herbs on drug metabolism; pharmacodynamic effects, herb-drug interactions that occur in the brain and other organ systems but are not predictable based on pharmacokinetic

principles of absorption and metabolism; and direct effects of herbs on the seizure threshold. Two principal pharmacologic systems are affected by herbs: the P450 and P-glycoprotein systems. The P450 hepatic enzyme enzymatic system may be induced or inhibited by medications including herbs. Several commonly used herbs interact with the P450 system (Table 2). This potentially results in unexpected (and unrecognized) subtherapeutic AED levels or toxicity. Foods also may affect the P450 system (eg, inhibition by grapefruit juice). Broccoli, charbroiled foods, and cigarettes are P450 inducers.

The other major pharmacokinetic system to consider vis-à-vis interactions is the transport system. Of the many transport systems, P-glycoprotein (Pgp) is the most thoroughly studied. Pgp is an adenosine triphosphate-dependent pump that extrudes substrates out of cells. Pgp is controlled by the multidrug-resistance gene MDR-1. Pgp contributes to the blood-brain barrier and limits the entry of drugs into the brain via the choroid plexus and cerebral endothelium. Pgp is also found in the intestinal epithelium, where it limits absorption from the gut. MDR-1 expression, and therefore Pgp transport, is affected by many naturally occurring compounds.[35] Herbs that affect Pgp are St John's wort, garlic, pycnogenol, and pipsissewa (Table 2).

Some herbs used for the treatment of epilepsy may interfere with the actions of drugs used for the treatment of other conditions. Betony, for example, has been shown to lower blood pressure and may exacerbate the effects of antihypertensive medications. Blue cohosh has hypoglycemic properties, thereby aggravating antidiabetic medications. Alcohol, benzodiazepines, and barbiturates may increase the toxicity of kava.[36] The impurity of some herbs may further lead to unpredictable results. Methylsufonylmethane (MSM), for example, is a nonprescription supplement with alleged antiepileptic effects. One of the ingredients in MSM is methsuximide,[37] once marketed as Celontin but largely abandoned in practice because of adverse effects.

Some herbs used to treat seizures, such as American hellebore, mistletoe, and scullcap, may actually exacerbate seizures (Table 3). Ginkgo, used to enhance cognition and prevent mental decline with aging, has been found to cause seizures in some individuals. Certain herbal oils (eg, eucalyptus, fennel, hyssop, pennyroyal, rosemary, sage, savin, tansy, thuja, turpentine, and wormwood) used for aromatherapy, cooking, and cleaning have been reported to cause seizures. These observations are based on oral consumption and transdermal absorption.

Although not an herbal drug, the ubiquitous compound caffeine has been associated with the aggravation of seizures.[38,39] Additionally, it has been used in the past to prolong seizures in patients receiving electroshock therapy. There is evidence that acute and chronic caffeine administration impairs the anticonvulsant activity of some AEDs in the murine maximal electroshock model.[40,41] Caffeine overuse should be avoided in persons with epilepsy.

Table 2 Effects of Herbs on Drug Metabolism

St. John's wort[42,43]	Controversial ? Inhibits Acutely ? Induces Chronically	Induces
Garlic[44]	Inhibits	Minimal interaction (? low to moderate inhibition)
Echinacea[45]	Inhibits	
Pycnogel[46]	Inhibits	Inhibits
Milk thistle	Inhibits	
American hellebore[47]		Inhibits
Mugwort	Inhibits	
Pipsissewa	Inhibits	Inhibits

Table 3 Effects of Commonly Used Herbs on Seizures

Herb	Effect on Seizures
Gingko	Proconvulsant[48]
Evening Primrose	Proconvulsant
Ephedra	Proconvulsant[49]
Mistletoe	Anticonvulsant Proconvulsant
American hellebore	Anticonvulsant Proconvulsant
Scullcap	Anticonvulsant Proconvulsant

Conclusion

Herbs that are commonly and consistently cited as effective treatments for epilepsy in the alternative medicine literature have been reviewed for their efficacy and safety data. Although these herbs are used to treat seizures, there is a lack of clinical or laboratory data supporting antiepileptic properties for 7 of the 9 commonly referenced products: American hellebore, betony, blue cohosh, mugwort, pipsissewa, scullcap, and valerian. Although laboratory data support antiepileptic effects for kava and mistletoe, objective data for clinical efficacy are unavailable. The lack of safety data, coupled with significant potential toxicities associated with each herb, make them difficult to recommend for the treatment of epilepsy. Additionally, several top-selling herbs, including those marketed to treat epilepsy, may provoke seizures.

Acknowledging the potential for herb-drug interactions is important in the management of epilepsy, and its implications should not be discounted as irrelevant. Herbs and supplements have variable actions on the metabolism, absorption, and transport of AEDs. Therefore, herbs may alter the effectiveness or side effects of the medications a patient is taking for epilepsy and may also directly affect the seizure threshold. Without sufficient data on efficacy, safety, or tolerability, it is difficult to adopt a recommendation supporting the use of herbal drugs in epilepsy. Still, patients should be encouraged to report the use of herbs and supplements in their medication history, and physicians should consider the implications that these drugs have on their patients' health.

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