

CRITICAL REVIEW AND INVITED COMMENTARY

Herbal medicine and epilepsy: Proconvulsive effects and interactions with antiepileptic drugs

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SUMMARY

The use of complementary and alternative medicine is on the rise, including among patients with epilepsy. Herbal medicine, one of the most popular forms of CAM, is considered to be both safe and effective by most consumers. Yet many herbs may increase the risk for seizures, through intrinsic proconvulsant properties or contamination by heavy metals, as well as via effects on the cytochrome P450 enzymes and P-glycoproteins, altering antiepileptic drug (AED) disposition. Herb–drug interactions may be difficult to predict,

especially since the quality and quantity of active ingredients are often unknown. Since most patients do not inform their physicians that they are taking herbal medicines, health care professionals must initiate a dialogue in order to prevent complications with the combined regimen. At the same time, further research is required regarding the effect of herbs on seizure activity and interactions with AED treatment.

KEY WORDS: Herbs, Epilepsy, Neurotoxic, Antiepileptics, Interaction, Drug disposition.

The use of complementary and alternative medicine (CAM) is on the rise, with rates of yearly CAM use reaching 42% in the United States (Eisenberg, 1997), 65% in Germany and 20% in the United Kingdom (Ernst, 2000). Herbal medicine is one of the most common forms of CAM, and patients generally consider this form of treatment to be both safe and effective (Eisenberg et al., 1998). Nearly one in six adults in the United States taking prescription drugs is also taking at least one herbal remedy (Kaufman et al., 2002), and patients aged 50 years and older use a mean of 2.66 herbal extracts on a daily basis, compared to a mean of 2.26 prescription drugs (Canter & Ernst, 2004).

Physicians may be unaware of CAM usage, including herbals, by their patients. Less than 40% of patients using CAM share this information with conventional physicians or emergency room staff (Eisenberg et al., 1998; Gulla & Singer, 2000). Patients who believe in the safety of the herbal medication they are taking are less likely to report

their use to their family physicians than those who do not (Giveon et al., 2004). Despite the possibility that certain herbs may cause severe or even lethal side effects (Ernst, 1998; De Smet, 2002), legislation requiring licensing for herbal remedies has been implemented in only a few countries, such as Germany, France, Sweden, and Australia. In the United States, the Dietary Supplement Health and Education Act of 1994 removed these products from Food and Drug Administration (FDA) jurisdiction.

Many patients with epilepsy turn to CAM therapies to supplement their medical regimen. A cohort study of 92 epileptics in Ohio found that 24% were using CAM therapies, of which 41% were using herbs and supplements. Only 31% (4/13 who responded to this question) replied that their neurologists were aware of their use of CAM (Peebles et al., 2000). A Nigerian study found that 47.6% of 265 epileptic patients were using only traditional African medicine (and no conventional medications), 24.1% combined traditional medicine with spiritual healing, and 20.4% spiritual healing alone. Many waited as long as 5 years prior to seeking conventional treatment, presumably when their seizures did not resolve (Danesi & Adetunji, 1994).

As many as one-third of epilepsy patients continue to exhibit signs of seizure activity in spite of medical treatment with antiepileptic drugs (AEDs) (Deckers et al., 2003), and

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herbal remedies have been considered a significant factor in many cases. Many herbs contain neurotoxic components that have been shown to induce seizures. Unsupervised herbs may be contaminated by heavy metals such as lead and arsenic, or may contain undisclosed quantities of conventional medications, even AEDs. And finally, herbs may affect the disposition of AEDs (i.e., absorption, distribution, metabolism, and excretion), thereby reducing their efficacy. This paper will review the literature (*Medline* search) and present the potentially harmful effects of herbal remedies and herb–drug interactions in patients with epilepsy.

HERBS ASSOCIATED WITH SEIZURES

Many herbs are known to affect the central nervous system, some with sedative effects (kava, valerian, passion flower, and chamomile) and others stimulating CNS function (ephedra and the caffeine-containing herbs coffee, tea, cocoa, cola, matē and guarana) (Spinella, 2001). The link between herbal remedies and seizure activity is compelling, though in humans only case reports have been published (Table 1). Perhaps the most famous example of herb-induced seizures is that of the artist Vincent van Gogh, who during the last two years of his life suffered from hallu-

cinatory convulsions. Many believe that his seizures were the result of the toxic effects of wormwood (*artemesia absinthium*), a herb used to distill alcohol, which contains the proconvulsant compound terpene thujone (Arnold, 1998). Epileptic seizures may also result from contamination of the herbal preparations with lead and other heavy metals (Saper et al., 2004), which may only be discovered through complex laboratory processes, unavailable to most consumers of herbal medicine. Herbal remedies may themselves contain AEDs (Lau et al., 2000), which may lead to toxic levels with what would otherwise be a therapeutic dose.

Herbs with epileptogenic components

There are a large number of herbs that contain neurotoxic compounds (Burkhard et al., 1999; Spinella, 2001), though not all have been shown to cause seizures in humans (Table 2). Evening primrose oil (EPO) is a popular herb used in the treatment of premenstrual syndrome, diabetic neuropathy, Sjogren's syndrome, and attention deficit/hyperactivity disorder. EPO contains the omega-6 fatty acid γ -linoleic acid (GLA), which is considered central to its healing effects but may, at the same time, lower the seizure threshold (Vaddadi, 1981; Miller, 1998). The herb Starflower (borage) is another source for GLA, and is used as a diaphoretic, expectorant, anti-inflammatory, and

Table 1. Case reports of herb-induced seizures

Herb	Reference	Patient (s)	Comments
Ephedra	Haller et al., 2005	19 cases	Of 20 cases "probably related" to dietary supplement use.
Eucalyptus	Burkhard et al., 1999	12-month-old girl	Bath with pine + thyme
Ginkgo biloba	Granger, 2001	78-old-year man, 84-old-year woman	Breakthrough seizure (valproate)
	Gregory, 2001	7 cases	FDA Special Nutritionals Adverse Event Monitoring System
	Kajiyama et al., 2002	2-old-year girl	Elevated serum MPN* (360 ng/mL)
	Kupiec & Raj, 2005	55-old-year male	Breakthrough seizure (on valproate + phenytoin)
	Miwa et al., 2001	36-old-year woman	Healthy
Pennyroyal	Anderson et al., 1996	24-old-year female 22-month-old girl Adult woman (age-?) 24-old-year female	To induce abortion Accidental ingestion To induce menses To induce menses
	Holland, 1902	24-old-year female	Healthy
	Kimball, 1898	23-old-year female	Healthy
	Bakerink et al., 1996	2 infants	From mint tea
	Yagi et al., 1993	21-month-old infant	Elevated serum MPN* (90 ng/mL)
Sage	Burkhard et al., 1999	54-old-year woman 53-old-year man	Given for hyperlipidemia Given for fatigue
Shankhapusphi (Ayurveda)	Dandekar et al., 1992	2 patients on phenytoin	
Star Anise	Gil Campos et al., 2002 Ize-Ludlow et al., 2004 Johanns et al., 2002 Vandenbergh et al., 2003	1-month-old girl 7 infants 16 patients 23-old-year man	Used for colic
Star Fruit	Chang & Yeh, 2004 Neto et al., 2003	72-old-year diabetic man on hemodialysis 7 uremic patients	Mortality rate from poisoning ranges from 20 to 40% (Chang and Yeh, 2004) Treated with hemodialysis

*MPN, 4-O-methylpyridoxine ("Ginkgotoxin"); detectable level, 15 ng/mL.

Table 2. Herbs and epilepsy: mechanism of action (see text)

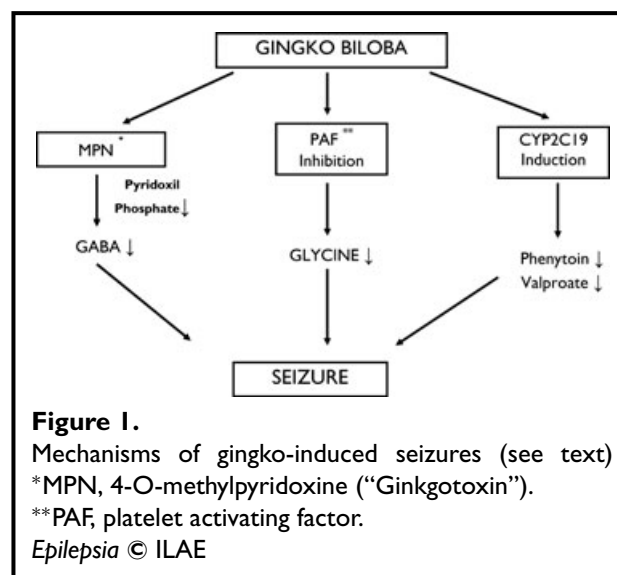
Herbs	Mechanism
With neurotoxic components	
Ephedra (ma huang)	Ephedra alkaloids can induce seizures, as well as predispose patients to both hemorrhagic and ischemic stroke (Bruno et al., 1993)
Evening primrose oil	γ -linoleic acid (GLA) reduces seizure threshold
<i>Ginkgo Biloba</i>	4'-O-methoxypridoxine ("Ginkgotoxin") found in seeds and leaves
Pennyroyal	(R)-(+)-pulegone induces seizures.
Star anise – Japanese (<i>Illicium anisatum</i>)	Anisatin is a known neurotoxin
Star anise – Chinese (<i>Illicium verum</i>)	Veanisatins A, B, C are neurotoxic at high doses; herb may be contaminated with anisatin.
Star fruit (<i>averrhoa carambola</i>)	Oxalate compound increases GABA uptake in the cerebral cortex of the rat (Neto et al., 1998; Fang et al., 2007)
Wormwood (<i>artemesia absinthium</i>)	Terpene thujone found in a number of herbs (Spinella, 2001)
Altering AED disposition	
<i>Ginkgo biloba</i>	Induces CYP2C19, reducing serum levels of phenytoin and valproate
Saint John's wort (<i>Hypericum perforatum</i>)	Inhibits CYP enzymes, induces intestinal Pgp; no effect on carbamazepine levels
Grapefruit	Inhibits CYP 3A activity; increases bioavailability of carbamazepine and diazepam
Shankhapusphi (ayurveda)	Decreased activity and serum levels of phenytoin
Sho-seiryu-to/sho saiko -to	Delayed gastric emptying in rats led to increased carbamazepine levels

galactagogue (Newall et al., 1997). Borage is also used in the treatment of fever, cough, and depression, and is reputed to act as a restorative agent on the adrenal cortex (Hoffman, 1987). Although it has been recommended to avoid the use of EPO and borage in patients with epilepsy (Miller, 1998), no cases of seizures with these herbs have been reported, and rat studies have found that GLA may even have antiseizure activity (Yehuda et al., 1994; Voskuyl et al., 1998).

Some herbs have clearly defined neurotoxic components that may precipitate seizures. Japanese star anise (*Illicium anisatum*) is a toxic plant grown in the south of Japan, which contains the neurotoxin anisatin, a potent noncompetitive GABA antagonist. Japanese star anise has been shown to cause picrotoxin-like convulsions in killifish, mice, and dogs (Kudo et al., 1981). Chinese Star Anise (*Illicium verum*) is a well-known spice, and is used as a carminative and sedative for the treatment of infant colic. Though considered to be safe and nontoxic, Chinese star anise contains compounds similar to anisatin—the veanisatins A, B and C (Okuyama et al., 1993; Nakamura et al., 1996), which, at high doses, can also cause seizures (Okuyama et al., 1993). Ize-Ludlow et al. found seven cases of star anise intoxication over a two-year period in the emergency department of Miami's Children's Hospital. Some of the neurological complications could be attributed to either an overdose of *I. Verum*, contamination with *I. Anisatum*, or a combination of the two (Ize-Ludlow et al., 2004). The herb Pennyroyal contains the monoterpene R-(plus)-pulegone, a compound that causes seizures when present in high concentrations (Gordon et al., 1982).

Other herbs may have a complex of mechanisms that may lead to seizures. *Ginkgo biloba* (ginkgo) has been used by the Chinese for centuries, usually as a remedy for chest ailments. Today ginkgo is widely used in the West for the

treatment of a number of conditions, primarily dementia and peripheral vascular disease (Le Bars et al., 1997; Pittler & Ernst, 2000; Canter & Ernst, 2002). Ginkgo can produce changes on computer-analyzed encephalography similar to those seen with the seizure-inducing drug Tacrine (Itil et al., 1996; Lebert et al., 1996). A number of mechanisms explaining the pro-epileptic effects of ginkgo have been proposed (Figure 1). Ginkgo contains the neurotoxin (termed "Ginkgotoxin") 4'-O-methoxypridoxine (MPN), one of several vitamin B6 derivatives with anti-vitamin properties. MPN indirectly inhibits γ -aminobutyric acid (GABA) formation via competitive antagonism of pyridoxil phosphate, a coenzyme of glutamate decarboxylase, the enzyme synthesizing GABA from glutamate (Shannon et al., 2003).



MPN can be found in both the seeds and the leaves of the plant (Arenz et al., 1996; Fiehe et al., 2000), and at toxic levels can precipitate repetitive seizures, due to enterohepatic excretion with elevated serum levels persisting for several hours (Kajiyama et al., 2002). The administration of pyridoxil phosphate has been shown to prevent or terminate convulsions caused by MPN (Gammon & Gummit, 1957). The number of Ginkgo seeds that may be eaten safely, by either adults or children, is unknown. Each seed contains approximately 80 μg of MPN (Arenz et al., 1996), while in those case reports of Ginkgo-associated seizures where MPN was measured, levels ranging from 90–484 ng/mL were found. Ginkgo may also cause seizures through antagonism of platelet aggregating factor (Kudolo et al., 2003), resulting in a central stimulant effect through blockade of the inhibitory neurotransmitter glycine (Manocha et al., 1996, 1997). The effects of ginkgo on AED disposition will be discussed below.

Herbs with neurotoxic contaminants

Unsupervised herbal remedies, including those sold widely in the United States, may contain neurotoxic material such as heavy metals, which may induce seizures. In an investigation of seizures reported among 19 infants (mean age of 3.8 months) treated with traditional medicines in Dubai (Al Khayat et al., 1997) seizures were found to be due to lead intoxication, as was the case in a 4-month-old infant in China (Chan et al., 1977). Other heavy metals such as arsenic, zinc, mercury, aluminum, and tin have been discovered in Ayurvedic herbal preparations, with serum concentrations reaching 10 times accepted toxic levels (Dunbabin et al., 1992; Pye et al., 1992; Thatte et al., 1993; Treleaven et al., 1993; Kew et al., 1993; Keen et al., 1994; Perharic et al., 1994; Sheerin et al., 1994; Bayly et al., 1995). A study of 70 ayurvedic herbal medicine products sold in the Boston area found that 20% contained potentially harmful levels of lead, mercury, and/or arsenic (Saper et al., 2004). Herbal remedies may also contain undeclared conventional medicines such as aspirin and paracetamol (Kshirsagar, 1993). A 33-year-old patient with epilepsy on a multidrug regimen (valproate, carbamazepine, and phenobarbital) took a Chinese proprietary antiepileptic medicine containing phenytoin, and was admitted to the hospital comatose. Serum phenytoin levels were found to be elevated (48.5 mg/L) to nearly 2.5 times the safe upper limit (19.75 mg/L) (Lau et al., 2000).

HERBS ALTERING AED DISPOSITION

Conventional medications are prescribed under the assumption that the designated drug will act in a predictable, dose-related manner. Yet many factors en route, from oral ingestion to target organ response, may affect the disposition of a drug and subsequently bioavailability and treat-

ment outcome. Any number of influences may affect drug disposition, including environment, genetic makeup, and concurrent illness (e.g., renal failure), which often render dose-response curves unreliable (Wilkinson, 2004). Herbs contain physiologically active substances that can significantly alter the response to AED treatment, even with accepted therapeutic doses (Table 2). The two main mechanisms by which herbs affect drug disposition are via cytochrome P450 enzymes and P-glycoproteins.

Cytochrome P450 enzymes

Cytochrome P450 (CYP) is a complex of oxidative enzymes responsible for the biosynthesis and degradation of endogenous compounds such as steroids, lipids and vitamins, found primarily in the liver. The most important enzyme is CYP3A, which accounts quantitatively for nearly 50% of CYP enzymes. CYP3A metabolizes a multitude of compounds from almost every drug class, and is thus involved in the metabolism of more than half of the therapeutic agents that undergo alteration by oxidation (Wilkinson, 2005).

A number of herbs have been found to alter drug metabolism through inhibition of the CYP system. A prime example is grapefruit juice (GJ), which is used internally by herbalists for gastrointestinal complaints and externally as a lymphatic stimulant, as well as for “lifting the spirits.” Furanocoumarins present in the fruit, primarily bergamottin and other furanocoumarin dimers, are the major contributors to a pronounced inhibitory effect on CYP3A4 activity (Ioannides, 2002). Bergamottin is converted to a reactive intermediate by CYP3A4, which then interacts covalently with the apoprotein moiety of the cytochrome, leading to the loss of activity (He et al., 1998). Carbamazepine is catalyzed primarily by CYP3A, though CYP2C8 can also make a substantial contribution (Kerr et al., 1994). A large glass (300 mL) of fresh GJ can significantly increase oral bioavailability of carbamazepine (from 6.55 to 9.20 $\mu\text{g}/\text{mL}$; Garg et al., 1998), and more than triple the bioavailability of diazepam (Ozdemir et al., 1998).

Herbs can affect other CYP enzymes as well. Ginkgo biloba induces CYP2C19, reducing serum levels of such drugs as phenytoin and valproate (Yin et al., 2004), while other herbs, such as the Chinese herb Bai Shao (white peony root), increase serum carbamazepine levels by enhancing absorption, and not through its effects on CYP activity (Chen et al., 2002). After observing two patients experience loss of seizure control, investigators evaluated the effect of the ayurvedic formula Shankhapushpi on phenytoin. They found that multidose administration of Shankhapushpi to lab rats decreased both plasma levels (from $9.62 \pm 2.93 \mu\text{mol}/\text{L}$ to $5.10 \pm 0.67 \mu\text{mol}/\text{L}$) as well as antiepileptic activity of the drug (Dandekar et al., 1992). Another study evaluated the decrease in drug efficacy by measuring maximal electroshock seizure (induced by administering a 150-mA current for 0.2 seconds to animals,

measuring abolition of tonic hind limb extension) in the presence of the ayurvedic remedy (Swinyard and Woodhead, 1982).

Not all herbs with significant *in vitro* effects on CYP activity necessarily affect drug levels *in vivo*. For example, anthraflavic acid, a phytoestrogenic compound found in *Polygonum cuspidatum* (Matsuda et al., 2001), inhibits CYP1A *in vitro*, while *in vivo* it upregulates hepatic expression of the enzyme when administered to rats (Ayrton et al., 1988). St. John's wort (SJW), a herb used for the treatment of depression, is produced from an extract of the plant *Hypericum perforatum*. SJW extracts inhibit cytochrome P450 enzymes belonging to all the xenobiotic-metabolizing families. The components hyperforin, hypericin, quercetin, and 13,II8-biapiogenin are believed to be responsible for this inhibitory effect (Obach, 2000). In most cases, inhibition by SJW is of a competitive nature, suggesting that these compounds serve as CYP450 substrates. *in vivo*, they can induce CYP450 expression as well, assuming that the necessary intracellular levels can be attained (Ioannides, 2002). However, SJW does not alter carbamazepine pharmacokinetics (Burstein et al., 2000). It has been suggested that the enzyme may have already been maximally induced by the repeated intake of the drug, or else that carbamazepine may not function as a substrate of PGP, which is also activated by SJW (Ioannides, 2002).

This same phenomenon is true for the benzodiazepine alprazolam, also metabolized by CYP3A yet also not affected by SJW (Markowitz et al., 2000). Other herbs, such as the Chinese herb Bai Shao (white peony root), increase serum carbamazepine levels by enhancing absorption, and not through effects on CYP activity (Chen et al., 2002). Two commonly used Japanese herbs (Sho-seiryu-to and Sho-saiko-to) can delay gastric emptying in rats, reducing absorption and subsequently serum levels of carbamazepine (Ohnishi et al., 1999, 2002).

P-glycoproteins

P-glycoproteins (Pgps), the gene product of MDR1, are transporter proteins found primarily in the intestines, gonads, kidneys, biliary tract, and central nervous system. Pgps are considered a prime candidate contributing to the unresponsive nature of multiple mechanism-unrelated AEDs (Crowe & Teoh, 2006). Pgps inhibit both intestinal absorption and transport to the CNS through the blood-brain barrier, with epileptogenic regions of the human brain having higher amounts of surface Pgp than other areas (Potschka & Loscher, 2001; Sisodiya et al., 2002). And though one study of nine AEDs found that only one drug, acetazolamide, was actually a Pgp substrate (Crowe & Teoh, 2006), other AEDs such as phenytoin, carbamazepine, phenobarbital, lamotrigine, gabapentin and topiramate are also believed to be Pgp substrates (Löscher & Potschka, 2005; Löscher, 2007).

Many herbs and their components can inhibit, activate, or induce Pgp activity. Curcumin, ginsenosides, piperine, some catechins from green tea, and sillymarin from milk thistle were found to be inhibitors of Pgp, while other catechins from green tea increased Pgp-mediated drug transport by heterotropic allosteric mechanism (Zhou et al., 2004). The GJ compounds bergamottin and quercetin modulate Pgp activity, while SJW induces intestinal expression of Pgp *in vitro* and *in vivo* (Zhou et al., 2004). A study of 10 patients with uncontrolled epilepsy were treated with phenytoin and evaluated for steady-state pharmacokinetics of the AED. Piperine, the active component of *Piper longum*, *Piper nigrum*, and *Zingiber officinalis*, significantly elevated mean plasma concentration of the drug, with a significant increase in AUC, C_{max} , and K_a (Pattanaik et al., 2006).

PREDICTING HERB-DRUG INTERACTIONS

Unlike conventional drug-drug interactions, which are usually familiar and predictable, herb-drug interactions are exceedingly difficult to anticipate. Herbs may have several generic names, which can easily lead to confusion. For example, the herb commonly known as "feverfew" (*tanacetum* or *chrysanthemum parthenium*) may also be referred to as "altamisa," "bachelors' button," "chamomile grande," "featherfew," "featherfoil," "febrifuge plant," "midsummer daisy," "mutterkraut," "nosebleed," "Santa Maria," "wild chamomile," or "wild quinine." The use of latin names, such as *taraxacum officinale* (celery) or *sygium aromaticum* (clove) may also make common herbs unfamiliar to most medical professionals, even more so with the use of Chinese nomenclature. Herbal formulas contain many herbs, and it is often impossible to know which herbs are present and at what concentrations, making the prediction of herb-drug interactions a daunting task.

Even if the name of the herb is familiar, the quantity and quality of active components are often difficult to predict. In a study of 50 commercially produced ginseng preparations, six contained no ginsenosides whatsoever, while the remaining 44 had ginsenosides levels ranging from 1.9% to 9.0% (Cui et al., 1994). Garlic preparations may also contain varying amounts of active components, depending on the mode of preparation (chopped, crushed, cooked, distilled, or homogenized in oil) (Lawson et al., 1992). Draves and Walder found that the percentage of active components in commercial tablets of SJW varied from 31.3% to 80.2% of the claim of active ingredients on the label (Draves & Walker, 2003). This may be explained by the fact that the hypericin content of SJW is subject to marked seasonal variations (Southwell & Bourke, 2001). Hyperforin, an active ingredient of SJW, is photosensitive, and other active components are unstable in aqueous solution, while

degradation is dependent on the pH of the solution (Ang et al., 2004).

CONCLUSIONS

No clear guidelines exist today for the use of herbal remedies by patients on antiepileptic treatment. In the United States, herbal remedies are considered to be food products by the FDA, allowing patients unlimited access, though recently finalized regulations will standardize the manufacturing process of dietary supplements (<http://www.npcicenter.com/anm/templates/newsATemp.aspx?articleid=18841&zoneid=18>) The National Center for Complementary and Alternative Medicine (NCCAM) fact sheet warns that consumers cannot assume that because a herbal supplement is “natural” it is safe or without harmful effects. The NCCAM goes on to recommend that anyone using a herbal supplement should “do so under the guidance of a medical professional, who has been properly trained in herbal medicine” (NCCAM). At the same time, physicians are being encouraged to try and accept the possible benefits of CAM, even those “therapies for which scientific support is anecdotal, equivocal or preliminary. . . . We as a profession must address the challenge of discussing alternative therapies with our patients and put an end to the “don’t ask, don’t tell” approach that characterizes communication in this area” (Eisenberg, 1997).

The link between herbal remedies and seizure activity may be compelling, but it is not conclusive. Even for conventional medications adverse effects can be difficult to assess, with many confounding variables leading to low levels of imputation agreements between decision algorithms (Macedo et al., 2003). How much more so when assessing harmful herb–drug interactions, where we have only limited laboratory findings and case reports. While herbs such as Japanese star anise (*Illicium anisatum*) should probably be avoided in all patients and not only in patients with epilepsy, Chinese star anise (*Illicium verum*) is probably safe for most, though for whom and at what levels is unclear. Without more information regarding these interactions, both in vitro and in vivo, the medical professional will continue to find it difficult to advise patients.

The first step in preventing complications of drug–herb interactions is for the physician to initiate dialogue with patients regarding current or intended use of herbal remedies. Next, carefully done studies, at least for the most commonly used herbs, should be undertaken in animal models of epilepsy and in laboratory studies of interactions with AEDs in order to evaluate their proconvulsant properties and effects on AED disposition. Unfortunately, research in the field of herbal medicine is not considered “economical” (Mashour et al., 1998), though organizations such as the NCCAM are funding such studies. Research should ex-

amine not only the benefits of herbal medicine, but also the interactions between herbal and conventional therapies, especially for antiepileptic medications whose therapeutic window is often narrow. Patient compliance with AED use and a clear understanding by both physician and patient as to potential interactions between the two may help prevent dangerous complications of the combined regimen. Patients should be able to benefit from the “best of both worlds” without increasing the risk of complications, either “chemical” or “natural.”

Disclosure/conflict of interest statement

No funding has been provided, and there are no conflicts of interest for any of the authors of this paper.

We confirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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