Botanicals and Herbs: A Traditional Approach to Treating Epilepsy

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Summary: Botanicals and herbs have a centuries-old tradition of use by persons with epilepsy, in many cultures around the world. At present, herbal therapies are tried by patients in developing as well as developed countries for control of seizures or adverse effects from antiepileptic drugs (AEDs), or for general health maintenance, usually without the knowledge of physicians who prescribe their AEDs. Well-designed clinical trials of herbal therapies in patients with epilepsy are scarce, and methodological issues prevent any conclusions of their efficacy or safety in this population. Furthermore, some botanicals and herbs may be proconvulsant or may alter AED metabolism. In spite of these limitations, further preclinical evaluation of botanicals and herbs and their constituent compounds using validated scientific methods is warranted based on numerous anecdotal observations of clinical benefit in patients with epilepsy and published reports showing mechanisms of action relevant to epilepsy or anticonvulsant effects in animal models of epilepsy. This review highlights the use of herbal therapies for epilepsy, outlines the role of the U.S. Food and Drug Administration in regulating herbal products, and presents the author's approach to the scientific assessment of herbal therapies as potential therapies for patients with epilepsy. **Key Words:** Epilepsy, herbal medicine, botanical, dietary supplement, complementary and alternative therapies, huperzine A.

INTRODUCTION

Despite the availability of many antiepileptic drugs (AEDs), nearly one in three patients with epilepsy who have access to AEDs continue to have seizures, and a similar proportion experience unacceptable AED-related adverse effects.[1] In addition, the large majority of people with epilepsy around the world are not under treatment with AEDs, largely because of their lack of access to physicians, the costs of AEDs, and cultural attitudes toward modern treatments.[2]

Over thousands of years, people with epilepsy have used a variety of botanicals and herbs, hereafter referred to simply as *herbal therapies* (although no clinical benefit is implied by this term). Today, herbal therapies are among the most commonly used forms of complementary and alternative medical (CAM) therapies by patients. The National Institutes of Health–National Center of Complementary and Alternative Medicine (NIH–NCCAM; http://nccam.nih.gov/) identifies CAM therapies as healthcare and medical practices that are not currently an integral part of conventional medicine—meaning the system of medical knowledge and practices taught in Western medical schools (for example, in the United States), and as practiced by Western-trained physicians, including neurologists.

Patients with a variety chronic illnesses, including epilepsy, take herbal therapies for many reasons. For example, patients in developed countries may view herbal therapies as natural and time-tested and therefore safe compared with what are perceived as artificial drugs—an attitude supported by recent reports of safety concerns associated with widely prescribed FDA-approved drugs. In developing countries, there may be access to herbal therapies but not to pharmaceuticals, because of cultural and economic factors.

Herbal traditions include traditional Chinese medicine, Ayurveda, and other culturally specific practices in which plant materials, processed or not, are ingested by persons with the intention of reducing symptoms or curing disease. This review focuses on the extent and patterns of use of herbal therapies by patients with epilepsy, regulatory considerations for dietary supplements (which include herbal therapies in the United States), safety issues, specific herbal therapies that have been used and evalu-

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ated for epilepsy, and a bench-to-bedside approach to herbal therapy research for epilepsy.

Extent and patterns of use

Developed countries. In developed countries, CAM treatments, including herbal therapies, are often used for general health maintenance or for chronic conditions, such as pain or epilepsy, that respond poorly or incompletely to standard treatments.[3] Liow et al.[4] surveyed 228 adult patients with epilepsy in the U.S. Midwest about their use of, perception of, and attitudes toward CAM therapies. Of these, 39% reported using CAM therapies, and 25% reported use specifically for seizure control. The most common forms of CAM were herbal therapies and other dietary supplements, prayer and spirituality, megavitamins (i.e., high-dose vitamins), chiropractic care, and stress management.

Other surveys in the United States or the United Kingdom suggest that up to one in three patients with epilepsy take herbal therapies, dietary supplements, or both, and that the majority do not inform their treating physicians[5-7]; this includes, for example, persons of South Asian origin living in the United Kingdom.[8] In one survey, the most frequently used were ginseng (*Panax* and *Eleutherococcus* species; less often, *Withania* species), St. John's wort (*Hypericum perforatum*), melatonin, ginkgo (*Ginkgo biloba*), garlic (*Allium sativum*), and black cohosh (*Actaea racemosa*).[6] In another study, garlic, ginkgo, soy (*Glycine max*), melatonin, and kava (*Piper methysticum*) were most often taken.[7] Ginkgo is commonly taken by nursing home residents, including those with epilepsy, and the potential for proconvulsant effects of ginkgo products is cause for concern.[9-11]

Clinical experience suggests that patients may try some herbal therapies in order to reduce AED-related adverse effects or comorbid conditions, such as valerian for insomnia, St. John's wort for depression, or ginkgo for memory disturbance. By inquiring whether patients are taking herbal therapies, physicians may gain insight into nonseizure-related problems that patients may be experiencing.

Developing countries. Herbal therapies for epilepsy in developing countries have evolved over the centuries, often in conjunction with changing cultural beliefs, systems of health care, and levels of education.[12,13] For example, nearly 40% of persons responding to a 1988 survey in China would suggest that a friend with epilepsy ask for an herbal medicine doctor or seek acupuncture.[14] Herbal therapies in developing countries are generally available from traditional healers or practitioners, whether instead of or in addition to medications prescribed by Western-trained physicians. It is not unusual in some regions for herbal therapies to be taken together with AEDs,[15] with combinations that can be tested experimentally in laboratory animals,[16] or after treatments prescribed by physicians fail to control seizures.[17]

Regulatory aspects

Governmental regulations concerning herbal therapies vary around the world. In the United States, prescription drugs are federally regulated by the Food, Drug, and Cosmetic Act, but herbal therapies by the 1994 Dietary Supplement and Health Education Act (DSHEA), under the auspices of the FDA's Office of Nutritional Products, Labeling, and Dietary Supplements, which is also responsible for developing policies for dietary supplements. DSHEA defines a dietary supplement as a product taken by mouth that contains a dietary ingredient intended to supplement the diet. The dietary ingredients in these products may include vitamins, minerals, herbs or other botanicals, amino acids, and substances such as enzymes, organ or glandular tissues, and extracts, concentrates, and metabolites (Overview of dietary supplements, Jan. 3, 2001: http://www.cfsan.fda.gov/~dms/ds-oview.html).

Under U.S. law, manufacturers of herbal therapies are responsible for the truthfulness of claims made on product labels and for controlling the quality of their products and verifying their safety. Manufacturers cannot claim effectiveness for a specific medical condition, such as epilepsy, but may claim an effect on a bodily part or function when the claim is accompanied by the following words: "This statement has not been evaluated by the FDA. This product is not intended to diagnose, treat, cure, or prevent any disease."

Under DSHEA, no government agency is required to verify the labeling claims of dietary supplements or to assess their quality and safety. Furthermore, dietary supplements, including herbal therapies, are not required to be produced according to standards of good manufacturing practices (GMP), which is the legal requirement for pharmaceutical products. Consequently, herbal therapies could potentially be contaminated, for example, with microorganisms or pesticides, or could contain potentially toxic levels of heavy metals, as has been documented for some Ayurvedic products,[18] or could be adulterated with other herbs or drugs.[19] In addition, the purity and amount of herbal extract or standardized presumed active ingredient per unit may vary significantly within the same bottle or from batch to batch, or from one branded herbal therapy product to another, because of variable manufacturing processes. Patients and many of their treating physicians are generally unaware of the potential for wide variability in purity and in per-dose quantity of herbal therapies.

Two recent developments are changing the role of the FDA role in overseeing the manufacturing and labeling of herbal therapies. First, in June 2007 the FDA issued a final rule, "Current Good Manufacturing Prac-

tice in Manufacturing, Packaging, Labeling, or Holding Operations for Dietary Supplements" (http://www.fda.gov/ohrms/dockets/98fr/cf0441.pdf), which significantly tightens manufacturing standards for dietary supplements, including herbal therapies, thereby ensuring their quality. Second, the FDA established a process to evaluate the safety and efficacy of herbal therapies (which they refer to as *botanical drug products*) in mitigating, treating, curing, or diagnosing a disease, which could potentially lead to FDA approval of herbal therapies for specific medical indications, including epilepsy. The first FDA approval of an herbal therapy under the new guidelines was, in late 2006, for an extract of green tea as a topical treatment of genital warts caused by the human papillomavirus (Verigen; http://www.fda.gov/cder/rdmt/InternetNME06.htm).

Safety issues

Despite generally being regarded as natural and therefore judged to be safe by the public, herbal therapies, like pharmaceuticals, may cause serious or life-threatening adverse effects[20]; furthermore, the long-term safety profile of most herbal therapies is unknown.[21,22] Numerous herbal therapies have been anecdotally reported to cause seizures, including in patients with epilepsy[23]; these include anisatin (a component of Japanese star anise, or *Ilicium anisatum*), which is used in Spain and other countries to treat infant colic,[24,25] ginkgo nuts,[26] essential oils,[27] evening primrose (*Oenothera* species) and borage (*Borago officinalis*),[27] and the stimulant ephedra (ma huang, or *Ephedra sinica*).[28] The extract of star fruit (*Averrhoa carambola*) may cause seizures in uremic patients[29]; it is used to induce seizures experimentally,[30] as is the extract from *Catha edulis* (khat), whose fresh young leaves are used recreationally by an estimated 5 million people in eastern Africa and the Arabian Peninsula.[31] Likewise, an extract of a Chinese herbal therapy for schizophrenia (*Coriaria* lactone, which is made from the active parts of the plant Loranthus on *coriaria sinica* Maxim) is the basis of a rat model for pharmacoresistant temporal lobe epilepsy.[32]

The pharmacokinetic interactions between herbal therapies and drugs, including AEDs, have been inadequately studied. Available evidence suggests that St. John's wort,[33] garlic, echinacea (various *Echinacea* species), pine bark extract (*Pinus pinaster*; also known as pycnogel, Pygenol, or Pycnogenol), milk thistle (*Silybum* species), American hellebore (*Veratrum viride*), ginkgo,[10,11] mugwort (*Artemisia* species), and pipsissewa (*Chimaphila umbellata*) affect the cytochrome P450 system and could therefore potentially affect serum concentrations of hepatically metabolized AEDs,[21-34] perhaps with fatal consequences.[10]

Herbal therapies for epilepsy

Historical evidence suggests that herbal therapies were used to treat convulsive seizures as early as 6000 BC in India, with the origin of Ayurveda,[35] and 3000 BC in China and in Peru; similarly, Africa and South America have rich traditions in herbal therapies, including for convulsions.[36-38]

The Ayurvedic literature contains treatises on epilepsy-like symptoms, causes, recognition, and treatment. Herbal and dietary therapies, which are recommended for external application, internal use, and topical use in the eyes and nose, include Brahmirasayan, Brahmighritham, Ashwagandha, old pure desi ghee, daily fresh juice of brahmi (*Centella asiatica* or *Bacopa* species, among others) with honey, garlic juice in oil, and powdered root of wild asparagus (*Asparagus racemosus*) with milk. Others are *Acacia nilotica* (syn. *Acacia arabica*), *Acorus calamus*, *Bacopa monnieri*, *Clitorea ternatea*, *Celastrus paniculatus*, *Convolvulus pluricaulis*, *Phyllanthus emblica* (syn. *Emblica officinalis*), mukta pishti (processed from pearls of *Mytilus magaritiferus* mussels), *Withania somnifera*.[39] Recent scientific publications provide the scientific rationale for proceeding with controlled trials of some of these herbal therapies in patients with epilepsy.[40,41]

The oldest Chinese document on epilepsy, The Yellow Emperor's Classic of Internal Medicine, Huang Di Nei Jing, dates in its earliest editions from 770 to 221 BC.[42] Herbal therapies used to treat convulsive diseases in Asia in modern times include Chai-Hu-Long-Ku-Mu-Li-Tan (TW-001), a mixture of extracts from 13 herbal therapies; *Gastrodia elata* (Tian Ma; gastrodia root); *Uncaria rhynchophylla* (cat's claw); *Menispermum dauricum* (moonseed); Shitei-To, a mixture of extracts from three medicinal herbs, Shitei (kaki calyx; the calyx of *Diospyros kaki* persimmon), Shokyo (gingerroot; rhizome of *Zingiber officinale*), and Choji (clove; pharmaceutical name, caryophylli flos; the flowerbud of *Syzygium aromaticum*); mixture of radish (*Raphanus sativus*) and pepper (*Piper* species, containing the alkaloid piperine); Qingyangshen (root of *Cynanchum otophyllum*); Kanbaku-taiso-to, a mixture of three herbal drugs, glycyrrhizae radix (licorice root; *Glycyrrhiza* species), tritici semen (wheat seed; *Triticum aestivum*), and zizyphi fructus (spiny jujube fruit; *Ziziphus spinosa*); paeoniae radix (peony root; *Paeonia lactiflora*, synonym *P. albiflora*); and Zheng Tai instant powder (a complex prescription of traditional Chinese medicines used for tonic–clonic seizures).[43] Several of these herbal therapies have been shown to have neuroprotective properties,[44-46] efficacy in animal models of epilepsy[47-49] and hippocampal slice models,[50] and effects on gene expression.[51] These studies generally do not specify, however, the methods used to 1) authenticate the source plants, 2) produce extracts

and fractions, 3) characterize the active ingredients, or 4) perform the preclinical evaluations.[43]

Recent investigations have addressed these limitations. For example, in their study of an extract of *Bacopa monnieri*, a traditional Ayurvedic therapy, on glutamate receptor binding and *GRIN1* gene expression (glutamate receptor, ionotropic, *N*-methyl-D-aspartate 1 gene; previously *NMDAR1*) in the hippocampus of rats after pilocarpine-induced seizures, Khan et al.[52] describe the source of the plant material, as well as the authentication and extraction methods. Furthermore, voucher specimens of the plant materials were prepared and stored, allowing for further characterization and replication of the findings.

In 2005, a comprehensive literature search identified 3 randomized controlled trials, 5 nonrandomized controlled trials, 6 case–control studies and 57 observational studies, including case reports, of herbal therapies from the East Asia for the treatment of epilepsy.[53] More than 135 different herbal extracts were used individually or in various combinations (formulas) in these studies, although rarely was the same herbal formula used in more than one study. The most frequently used plant (or animal) extracts were from the species *Pinellia ternata* (Ban Xia), *Arisaema serratum* (synonym *A. japonicum*; Tian Nan Xing), *Acorus calamus* (Shi Chang Pu), *Gastrodia elata* (Tian Ma), *Buthus martensii* (Quan Xie; bark scorpion), *Wolfiporia extensa* (synonym *Poria cocos;* Fu Ling), *Bombyx mori* (Jiang Qiang; silkmoth; the pharmaceutical name, bombyx batryticatus, indicates silkmoth infestation with a particular fungus), *Citrus reticulata* (Chen Pi), *Uncaria rhynchophylla* (Gou Teng), *Glycyrrhiza glabra* (Gan Cao), and *Salvia miltiorrhiza* (Dan Shen), as well as *Scolopendra subspinipes* (centipede), *Bupleurum falcatum*, *Succinum* (processed amber), *Paeonia lactifolia* (synonym *P. albiflora*), *Panax ginseng*, *Perichaeta communissma* (earthworm), and *Curcuma longa*.[43] The clinical studies were generally limited by methodological issues in study design, inadequate powering, insufficient categorization of seizure types and epilepsy syndromes, questionable choices of outcome measures and statistical methods, and lack of characterization of the herbal extracts. Only one clinical epilepsy study of an herbal extract has been published since 2005 in the English literature.[54]

Harvard epilepsy botanical program

Although properly controlled clinical evidence to support the use of specific herbal therapies for patients with epilepsy is lacking, available anecdotal and laboratory-based evidence suggests that further evaluation is warranted. Therefore, a program was established at Harvard Medical School to support preclinical evaluation of herbal therapies for epilepsy. The goals of the program are 1) to identify herbal therapies and compounds isolated from them that have promising activity in animal epilepsy models and relevant *in vitro* assays, 2) to conduct the preclinical studies necessary to proceed with early stage clinical studies, and 3) to plan and initiate these clinical studies.

In pursuit of these goals, collaborations were established with herbal experts and natural product chemists in East Asia, South America, and Africa, in order to 1) identify herbal therapies for evaluation (based on clinical recommendations of herbal experts, electronic database searches, review of original text references, and published results of laboratory or clinical studies) and 2) to test crude extracts and selected fractions of these herbal therapies, as well as pure compounds isolated from those fractions, in well-validated animal models of epilepsy and *in vitro* assays.

Although the most common reasons for selecting herbal therapies for preclinical evaluation have been either a tradition of use for seizures or known mechanisms of action that are relevant to epilepsy, epidemiological observations may also be helpful. For example, Salih and Mustafa[55] reasoned that the lower prevalence of epilepsy among school children of Khartoum province, Sudan, compared with that in Europe and North America may be related to frequent dietary ingestion of broad beans (*Vicia faba*). The authors therefore prepared an extract of *Vicia faba* and found that it blocked seizures in a mouse strychnine model.

To date, more than 30 herbal extracts and extract-derived compounds isolated from Chinese, Japanese, and Indian herbal therapies have been studied by the Harvard program in animal models of epilepsy through the National Institute of Neurological Disorders and Stroke (NIH–NINDS) Anticonvulsant Screening Project (ASP), and many have also been evaluated using *in vitro* assays of neuronal receptor or ion channel function. Approximately two-thirds of these extracts and extract-derived compounds show activity *in vitro*, *in vivo*, or both. An example is huperzine A.

Huperzine A. Based on its proposed action as a noncompetitive NMDA receptor antagonist,[56] huperzine A was selected for further evaluation as a potential anticonvulsant. Huperzine A is a sesquiterpene lycopodium alkaloid, typically isolated from Chinese club moss (*Huperzia serrata*); in Chinese folk medicine it is known as *qian ceng ta*. The chemical name for huperzine A is [5*R*-(5α,9β,11*E*)]-5-amino-11-ethylidene-5,6,9,10-tetrahydro-7-methyl-5,9-methanocycloocta[*b*]pyridin-2(1*H*)-one. The molecular formula is $C_{15}H_{18}N_2O$, and the molecular weight is 242.32.

Huperzine A has been traditionally used in China for the treatment of swelling, fever and inflammation, blood disorders, and schizophrenia,[57] and it is currently used in China for Alzheimer's disease. Huperzine A was classified as a dietary supplement by the FDA in 1997. It is

available in health food stores or via the Internet, labeled as a memory aid, and was recently studied in a multicenter NIH-sponsored trial for Alzheimer's disease at dosages up to 400 μg b.i.d. (http://clinicaltrials.gov/ct/show/NCT00083590?order=9; accessed December 17, 2008).

Huperzine A (ADD 357133) was submitted to the ASP and found to be potently active against subcutaneously administered pentylenetetrazol-induced seizures and less so against maximal electroshock-induced seizures after oral administration to Swiss–Webster mice, with peak anticonvulsant activity at 1 hour.[58] At doses of 1, 2, and 4 mg/kg, a maximum of 62.5% protection was observed. Impairment on the rotarod test was observed in 75 and 100% of mice tested at doses of 2 and 4 mg/kg, respectively. The TD_{50} was 0.83 mg/kg.

In the 6-Hz model, ED_{50} values for intraperitoneal huperzine A were 0.28, 0.34 and 0.78 mg/kg for 22, 32, and 44 mA, respectively, suggesting a possible advantage over phenytoin, carbamazepine, lamotrigine and topiramate, each of which display limited efficacy in this model at doses devoid of behavioral toxicity.[59] The less than twofold ratio of dosages effective across the range of current strengths suggests a further possible advantage over other drugs that are active in this model, such as levetiracetam.

SUMMARY

Despite the widespread use of herbal therapies by patients with epilepsy, there is a striking lack of controlled evidence to support their use, and anecdotal reports suggest that some herbal therapies may pose a safety risk to this population. Absence of proof, however, is not necessarily proof of absence, and the centuries-old traditions of use of herbal therapies for epilepsy provide a reasonable basis for systematically proceeding with preclinical assessments using modern scientific methods. Indeed, preclinical work at Harvard and elsewhere based on this approach suggests that the study of herbal therapies and herbal-derived compounds may yield promising candidates for further clinical development.

Herbal therapies may, therefore, potentially yield new treatment options for patients whose seizures are uncontrolled despite available AEDs, and may also represent inexpensive, culturally acceptable treatments for the millions of people around the world with untreated epilepsy.

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