



Review

Review of the use of botanicals for epilepsy in complementary medical systems – Traditional Chinese Medicine

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ABSTRACT

In traditional Chinese medicine, botanical remedies have been used for centuries to treat seizures. This review aimed to summarize the botanicals that have been used in traditional Chinese medicine to treat epilepsy. We searched Chinese online databases to determine the botanicals used for epilepsy in traditional Chinese medicine and identified articles using a preset search syntax and inclusion criteria of each botanical in the PubMed database to explore their potential mechanisms. Twenty-three botanicals were identified to treat epilepsy in traditional Chinese medicine. The pharmacological mechanisms of each botanical related to antiepileptic activity, which were mainly examined in animal models, were reviewed. We discuss the use and current trends of botanical treatments in China and highlight the limitations of botanical epilepsy treatments. A substantial number of these types of botanicals would be good candidates for the development of novel AEDs. More rigorous clinical trials of botanicals in traditional Chinese medicine for epilepsy treatment are encouraged in the future.

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1. Introduction

Epilepsy is a serious and complex set of neurological conditions, which affects 65 million individuals worldwide, and more than 85% of these patients live in developing countries [1]. Although the majority of patients with epilepsy will achieve remission, seizures in up to 30% will become drug-resistant despite treatment with adequate doses of appropriate antiepileptic drugs (AEDs) [2]. Furthermore, approximately 30–40% of patients with epilepsy suffer from numerous side effects from the standard AEDs. In the context of this predicament, there is a constant search for novel modes of treatment [3]. Over thousands of years, individuals with epilepsy have used a variety of botanicals and herbs, which are considered natural and are generally regarded as safe in many instances. Botanical therapies may 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 individuals worldwide with untreated epilepsy [4].

China has had rich traditions regarding botanical therapies for epilepsy for thousands of years. The first known document regarding epilepsy in China appeared in the Yellow Emperor's classic of internal

medicine, *Huang Di Nei Ching*, written by a group of physicians between 770 and 221 B.C. The description of epilepsy in this book, and in many other subsequent publications, was confined to generalized convulsive seizures. No documentation of absence or simple partial seizures was noted. The first classification of epilepsy, likely by Cao Yuan Fang in 610 A.D., listed five types of epilepsy: ‘Yang Dian’, ‘Yin Dian’, ‘Feng (Wind) Dian’, ‘Shih (Wet) Dian’, and ‘Ma (Horse) Dian’. Nevertheless, these five ancient classifications have no relation with the modern classification. From a traditional Chinese medicine (TCM) perspective, seizures are directly caused by Liver Yang Rising. Liver Yang Rising generates Heat, which flares up and disturbs the brain and Shen (Mind), and thus, leads to Internal Wind (seizures). Liver Yang Rising can be caused by Liver Yin Deficiency, Liver Blood Deficiency, Phlegm, Blood Stagnation and Liver Fire. Liver Qi Stagnation can also trigger Liver Yang Rising. In addition, ‘Yin Dian’, ‘Feng (Wind) Dian’, ‘Shih (Wet) Dian’, and ‘Ma (Horse) Dian’ indicate the different causes of seizures [5]. The treatment of epilepsy based on the principles of ‘Yin Yang Wu Xing’ consisted of herbs, acupuncture, massage, food therapy, and therapeutic exercise [6]. Traditional Chinese botanical medicine, which is often considered to be a gentle and safe alternative to synthetically manufactured drugs, is the most widely practiced form of herbalism worldwide. Traditional Chinese botanical medicines are obtained or synthesized from natural plants. Typical traditional Chinese botanical treatment uses one type of botanical as the basic drug to treat the major disease problem. This botanical is subsequently mixed with other botanicals to treat additional symptoms, which creates a multifunction formula for the disease. However, botanical medicine is an area of TCM that is readily amenable

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to empirical research. Most botanicals have only been examined in animal models for antiepileptic effects without adequate evidence from controlled clinical trials. Few articles have focused on a single botanical used by traditional Chinese medical practitioners, which may possess the antiepileptic/anticonvulsant effects.

In this review, we investigated botanicals that were used in TCM as treatments for epilepsy. We listed the most frequently used botanicals by traditional Chinese medical practitioners and discussed the potential mechanisms of their antiepileptic/anticonvulsant activities.

2. Methods

We searched online Chinese databases, including Wanfang, Weipu, and CNKI, using the Chinese characters “中药”, “草药”, “中草药”, “癫痫”, which represent the botanicals used for the treatment of epilepsy. We hand searched the Journal of Chinese Integrative Medicine, Chinese Medical Journal, Chinese Journal of Internal Medicine, Chinese Journal of Integrated Traditional and Western Medicine, Chinese Journal of Integrative Medicine, and other traditional Chinese medicine journals for the botanicals used solely or in a formula to treat epilepsy. We subsequently searched the PubMed online database using terms that included “botanical”, “herbal”, “epilepsy”, “seizure”, “TCM”, and “traditional Chinese medicine” and identified articles that used the preset search syntax of each botanical and inclusion criteria.

We searched the reference lists of all relevant papers for additional studies. In addition, we contacted colleagues and experts in the field to identify unpublished or ongoing studies. There was no language restriction in the search or inclusion of studies.

3. Results

The sources consulted in this work noted that 23 botanicals were used in Chinese traditional medicine to treat epilepsy. We reviewed the latest Chinese pharmacopeia [7] to determine whether there is a monograph for these Chinese medicines. Table 1 presents their names, Chinese names, and main active components.

In the following sections, the results of tests performed on 23 botanicals have been summarized; attention was focused on their anticonvulsant activity.

3.1. *Cynanchum otophyllum* (qingyangshen)

Qingyangshen is a traditional Chinese medicine that consists of the root of *C. otophyllum*, which is one of the most important medicinal plants used in southwest China to treat epilepsy. Two C-21 steroidal saponins, otophyllside A and B, were identified as its main active constituents that exhibit anticonvulsant activities [8]. Recently, five additional polyhydroxypregnane glycosides were isolated from the roots of *C. otophyllum* and exhibited neuroprotective activity against homocysteic acid-induced cell death in a dose-dependent manner [9]. Previous studies have demonstrated that *qingyangshen* has antiepileptic properties and a therapeutic effect on kainic acid (KA)-induced experimental seizures [10,11]. In addition, its modulatory effect in the cotreatment with diphenylhydantoin sodium (DPH) inhibits hippocampal c-fos expression in rats during seizures, which was suggested to be associated with KA-induced seizures [11]. It has been postulated that *qingyangshen*, when used in combination with PHT, may reduce the early production of fos protein, which thereby inhibits the secondary gene transcription that would contribute to the intracellular responses that lead to acute seizures [11]. A product based on *C. otophyllum* extract has previously been developed by the Yunnan Baiyao Group together with the Kunming Institute of Botany, Chinese Academy of Sciences.

3.2. *Scutellaria baicalensis* (huangqin)

Scutellaria baicalensis or *huangqin* is a famous botanical medicine in the Shanxi Province, which is in the northwest of China. Baicalin, the major flavonoid in the *S. baicalensis*, possesses anticonvulsant effects. The pharmacological profile of baicalin was explored in mice in recent studies [12–14], and it has been discovered to possess remarkable anticonvulsant and neuroprotective effects on pilocarpine-evoked status epilepticus (SE) in adult SD rats [14]. Furthermore, the anticonvulsant effect may be ascribed to the protection of endogenous enzyme levels, an increase in the GABA level in the brain, and inhibition of oxidative injury [12].

3.3. *Gastrodia elata* (tianma)

Gastrodia elata or *tianma* is primarily found in the mountainous ranges of China. The Chinese pharmacopeia lists this compound as an anticonvulsant, analgesic, and sedative effective against vertigo, general

Table 1
Botanicals in traditional Chinese medicine used in epilepsy therapy.

Generic name	Scientific name	Pinyin/Chinese name	Main active components
<i>Cynanchum otophyllum</i>	<i>Cynanchum otophyllum</i>	<i>Qingyangshen</i> /青阳参	Otophyllside A and B (C-21 steroidal saponin)
<i>Radix scutellariae</i>	<i>Scutellaria baicalensis</i>	<i>Huangqin</i> /黄芩	Baicalin
<i>Rhizoma gastrodiae</i>	<i>Gastrodia elata</i>	<i>Tianma</i> /天麻	Vanillin
<i>Radix bupleuri chinensis</i>	<i>Bupleurum chinense</i>	<i>Chaihu</i> /柴胡	Saikosaponin A
<i>Rhizoma coptidis</i>	<i>Coptis chinensis</i>	<i>Huanglian</i> /黄连	Berberine
<i>Nandina</i>	<i>Nandina domestica</i>	<i>Nantianzu</i> /南天竹	Nantenine
<i>Piper</i>	<i>Piper nigrum</i>	<i>Hujiao</i> /胡椒碱	Piperine
<i>Ramulus uncariae cum uncis</i>	<i>Uncaria rhynchophylla</i>	<i>Gouteng</i> /钩藤	Rhynchophylline, isorhynchophylline
<i>Herba centellae</i>	<i>Centella asiatica</i>	<i>Jixuecao</i> /积雪草	N-hexane, ethyl acetate, n-butanol
Saffron	<i>Crocus sativus</i>	<i>Zanghonghua</i> /藏红花	Safranal
<i>Ginkgo biloba</i>	<i>Ginkgo biloba</i>	<i>Yinxyngye</i> /银杏叶	Bilobalide
<i>Rhizoma acori tatarinowii</i>	<i>Acorus tatarinowii</i>	<i>Shichangpu</i> /石菖蒲	Asarone
<i>Radix salviae miltiorrhizae</i>	<i>Salvia miltiorrhiza</i>	<i>Danshen</i> /丹参	Hydrophobic tanshinone
Ginger	<i>Zingiber officinale</i>	<i>Jiang</i> /姜	Zingerone
<i>Matricaria recutita</i>	<i>Matricaria chamomilla</i>	<i>Muju</i> /母菊	Apigenin
<i>Licorice root</i>	<i>Glycyrrhiza glabra</i>	<i>Gancao</i> /甘草	Licorice flavonoid
Turmeric	<i>Curcuma longa</i>	<i>Jianghuang</i> /姜黄	Curcuminol
<i>Radix paeoniae rubra</i>	<i>Paeonia lactiflora</i>	<i>Chishao</i> /赤芍	Paeoniflorin
<i>Semen ziziphi spinosae</i>	<i>Ziziphus jujuba</i>	<i>Hongzao</i> /红枣	Sanjoinine A
<i>Radix astragali</i>	<i>Astragalus mongholicus</i>	<i>Huangqi</i> /黄芪	Saponin
<i>Radix ginseng</i>	<i>Panax ginseng</i>	<i>Renshen</i> /人参	Ginsenoside
All-grass of Snakefoot clubmoss	<i>Huperzia serrata</i>	<i>Shezhushishan</i> /蛇足石杉	Huperzine A
<i>Rhizoma pinelliae</i>	<i>Pinellia ternata</i>	<i>Banxia</i> /半夏	<i>Pinelliae</i> alkaloids

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