Mechanisms of natural products as potential antiepileptic drugs

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Abstract: The universal epileptogenic cascade remains unknown, and most modern treatments focus on the reduction of symptoms and the prevention of seizure recurrence. Experimental studies have demonstrated that herbal medicines may act as antiepileptogenic agents. In this study, the possibilities of plants with antiepileptic properties were reviewed and discussed on their structures and related mechanism of actions. This work constituted a literature review of medicinal plants showing antiepileptic properties by literature searching in Science Direct, PubMed and Wiley Online Library. The keywords of search included epilepsy, antiepileptogenesis, antiepilepsy, natural compounds, extract, herbal medicines and medicinal plants in epilepsy treatment. Only articles published in English were reviewed. Mechanism of action of the natural plants were described according to experimental studies. From the databases, we found 135 natural plants with antiepileptic properties. In this review, the highly studied natural plants were selected. These included Acorus calamus, Bacopa monnieri, Boerhaavia diffusa, Curcuma longa, Gastrodia elata, Ginseng, Uncaria rhynchophylla, Pinellia ternatae, Withania somnifera, Magnolia bark and Resveratrol-related products. From the evidences, natural products may potentially be developed as antiepileptic or antiepileptogenic agents. However, several issues in drug development should be considered such as safety, formulations, pharmacokinetic characteristics and possible interactions.

Keywords: Epilepsy, epileptogenesis, herbal medicines, medicinal plants.

INTRODUCTION

Epilepsy is known as one of the most common neurological conditions. According to the International League against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE) (2017), epilepsy is a defect in the brain characterized by an enduring predisposition to generate epileptic seizures and by the neurobiological, cognitive, psychological and social consequences of this condition (Fisher et al., 2017). Epilepsy requires the occurrence of at least one epileptic seizure. Epileptic seizure is defined as a transient occurrence of signs or symptoms due to a primary change to the electrical activity (abnormally excessive or synchronous) in the brain (Fisher et al., 2017; Lux et al., 2004). It is chronic disease with physical, psychological and socioeconomic consequences that may compromise a patients’ quality of life.

Side effects associated with antiepileptic drugs (AEDs) are also common, and patients at higher risk are those who need a larger amount and a higher dosage of AEDs (Kang et al., 2019). Newer generation of AEDs have helped improve seizure control and minimize side effects for many epileptic patients, but nevertheless, there are limitations reported for both the old and new AEDs. Firstly, around 30% of all patients with epilepsy are medically refractory epileptic patients (Kwan and Brodie, 2006; Kwan and Brodie, 2000). Secondly, current medications primarily act only to symptomatically suppress seizures (Acharya et al., 2008). Clinical evidence is limited in supporting the AEDs in correcting abnormalities that cause epilepsy (Temkin, 2001).

Therefore, newer drug therapies that are effective against drug-resistant seizures, possess favourable side effect characteristics, especially regards to neurological and psychiatric effects, are clearly needed. This review focuses on identifying natural products with antiepileptogenic potential to prevent or interrupt the initial mechanistic event of epilepsy and the safety issues of these products.

MATERIALS AND METHODS

This work constitutes a literature review of medicinal plants showing antiepileptic properties by literature searching in Science Direct, PubMed and Wiley Online Library. The keywords of search included epilepsy, antiepileptogenesis, antiepilepsy, antiepileptogenic, natural compounds, extract, herbal medicines and medicinal plants in epilepsy treatment. Only articles published in English were reviewed.

Pathogenesis of epilepsy

Currently, AEDs available in the market act primarily on the end-stage of the molecular mechanisms that generate the symptoms of epilepsy or the seizures themselves (Wong, 2010). Seizure reduction with current AEDs are accomplished by variety of mechanisms, including

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blockade of voltage-gated channels such as sodium and calcium, enhancement of inhibitory gamma-aminobutyric acid (GABA) impulses and interference with excitatory glutamate transmission. Many AEDs are found through screening assays that assessed the efficacy against acutely provoked seizures in non-epileptic animals. Thus, they inhibit seizures directly by decreasing neuronal excitability, such as by modulating neurotransmitter receptors and ion channels (Wong, 2010).

Epileptogenesis describes a process that begins with an initial insult such as trauma to the brain and is presumed to involve a cascade of secondary epileptogenic events (Giblin and Blumenfeld, 2010; Rakhade and Jensen, 2009; Bragin et al., 2000), and ends when the first generalized behavioural seizure is observed (Pitkanen, 2010; Walker et al., 2002). Epileptogenesis may also include the possibility of a never-ending process of clinical progression involving changes in seizure frequency and development of a refractory state (Dudek and Staley, 2011; Pitkanen and Lukasiuk, 2011; Mani et al., 2011).

Cellular alterations of epilepsy and their distributions are best characterized in the hippocampus (Mani et al., 2011). These changes are also accompanied by a variety of molecular changes. Examples are neurodegeneration, neurogenesis, gliosis, invasion of inflammatory cells, axonal sprouting, axonal injury, dendritic plasticity, angiogenesis, and changes in the extracellular matrix and alteration in voltage and ligand-gated ion channels in individual neurons. Consequently, several functional impairments develops, these include development delay, memory impairment, emotional impairment, behavioural impairment, somatomotor decline, and drug refractoriness. During the entire epileptogenic process, these alterations are subject to modulation by genetic background, epigenetic factors and developmentally regulated genetic programs (Mani et al., 2011).

Unless a key universal epileptogenic cascade can be identified, it is likely that different types of epilepsy will require different mode of preventive strategies (Jain, 2005). Therefore, identification of specific mechanisms will be helpful in optimizing treatments, leading to targeted therapies which are more effective than those currently available in the market.

**Natural products in seizure management**

Studies have shown that the majority of patients with epilepsy are not treated with AEDs, largely due to lack of access to physicians, cost of AEDs, and attitudes toward modern treatments (Meinardi et al., 2001). An intermediate pragmatic approach is to utilize natural products or extracts traditionally known to be useful for anti-seizure activity. This stimulates interest in investigating potential benefit of compounds or extracts derived from plants that may have medicinal applications for seizure but mechanism of action of these treatments remains unclear.

Only 2% to 44% of these patients reported using these products specifically for the control of seizures, others were for known comorbidities related to epilepsy such as depression, or to treat common AED adverse events such as impaired memory (Dana and Schacter, 2010). Over 135 different herbs have been reported to be used in a single or in 80 different combination formulae for the treatment of seizures (Schacter, 2009). The frequently used herbs include *Pinella ternata*, *Arisaema japonicum*, *Acorus calamus*, *Gastrodia elata*, *Buthus martenssi*, *Poria cocos*, *Bombex barryticatus*, *Citrus reticulata*, *Uncaria rhynchophylla*, *Glycyrrhia glabra*, *Salvia miltiorrhiza*, *Bupleurum falcatum*, *Paeonia albißora*, *Panax ginseng* and *Curcuma longa* (Schacter 2009; Schacter et al., 2008; Schacter, 2008). Ayurvedic practitioners use mixtures of natural products for epileptic patients and these usually contain herbal extracts, as well as animal ghee, honey and sometimes milk. The herbal extracts are also prepared from *Acacia arabica*, *Acorus calamus*, *Bacopa monnieri*, *Clitorea turutae*, *Celastrus panniculata*, *Convululus pluricaulis*, *Emblica officinalis*, *Mukta pishi* and *Withania somnifera* (Schacter, 2008; Kulkarni and Dhir, 2008). However, only 11 plants were chosen for this paper because they are well studied and documented. There is no hard evidence that recommends the use of complementary and alternative medicine (CAM) for the treatment of epilepsy (Li et al., 2009). Nevertheless, many extracts used for control of seizure in CAM, are being tested alone and in combination for antiepilepsy effects in animal models of epilepsy (Dana and Schacter, 2010).

**Fig. 1:** Chemical structure of α-asarone (one of major constituents in *Acorus calamus*).

**Acorus calamus**
*Acorus calamus* Linn. (family: Acoraceae, Ayurvedic name: ‘Vacha’) is a semi-aquatic, perennial, aromatic herb with creeping rhizomes. The ethyl acetate extract of *Acorus calamus* was found to be a potent antioxidant by inhibition of 1,1-diphenyl-2-picyrylhydrazyl free radical (Acuna et al., 2002). The roots and rhizomes of *Acorus calamus* have been used in ancient systems of medicine for the treatment of various neurological disorders (Hazra et al., 2007). *Acorus calamus* (fig. 1) possesses the ability to prevent the development of FeCl₂-induced epileptogenesis by modulating antioxidant enzymes such
as superoxide dismutase (SOD) and catalase (CAT), which in turn exhibit the potential of *Acorus calamus* to be developed as an effective AED (Hazra *et al*., 2007).

![Fig. 2: Chemical structure of Bacoside-A,B and C](image1)

Additionally, it may also inhibit lipid per oxidation (LPO) and tumor markers (Rohini *et al*., 2004).

**Boerhaavia diffusa**

*Boerhaavia diffusa* contains several phytoconstituents such as flavonoids, alkaloids, steroids, triterpenoids, lipids, lignins, carbohydrates, proteins, glycoproteins, punarnavoside (fig. 3), liriodendrin (fig. 3), punarnavine, boeravinones A-F (fig. 4), hypoxanthine 9-1-arabinofuranoside and ursolic acid (Sahu *et al*., 2008). One of the mechanisms that generate seizure is by activation of voltage-gated channels such as calcium. Liriodendrin presents in the methanolic extract of *Boerhaavia diffusa* roots showed calcium channel antagonistic activity (Mandeep and Rajesh, 2011). This mechanism may explain the benefits of *Boerhaavia diffusa* roots in epilepsy treatment (Mandeep and Rajesh, 2011).

**Curcuma longa**

The rhizomes of *Curcuma longa* have been cited in the literature on Indian medicinal plants for the treatment of epilepsy (Sharma *et al*., 2001). Several earlier studies using a raw extract of *Curcuma longa* showed the ability to prevent nerve damage, to reduce the progression of Alzheimer’s disease (Ringman *et al*., 2005), to inhibit MAO-A and B and to enhance brain monoamine levels (Yu *et al*., 2002). Curcumin (fig. 5), the yellow pigment isolated from this medicinal plant, (Ammon and Wahl, 1991) exhibits antioxidant, anti-inflammatory and anticarcinogenic properties (Bhowmik *et al*., 2009; Ammon and Wahl, 1991). These properties enhanced research in curcumin as a potential pharmacologic agent for many diseases (Hatcher *et al*., 2008). For example, curcumin has been shown to inhibit acute seizures and neuronal cell death in kainic acid (KA) animal models through radical scavenging and SOD-like activities (Peng *et al*., 2009; Sumanont *et al*., 2004). Curcumin can reduce the severity of seizures by affecting the histone modification of chromatin (Sng *et al*., 2006). Correlative data suggest that the antioxidant properties of curcumin such as its effects on LPO and protein oxidation, might account for a neuroprotective effect, but other multiple mechanisms could also be involved (Iyoti *et al*., 2009). Other studies have shown neuroprotective effects of curcumin against cerebral ischemic injury or traumatic brain injury (Shin *et al*., 2007; Wu *et al*., 2006; Wang *et al*., 2005). Curcumin blocks the signalling pathway into apoptotic cell death and indirectly affects the blood brain barrier for the prevention of neuronal cell death (Sng *et al*., 2006).

**Gastrodia elata**

*Gastrodia elata* is a traditional herb that has been used as an AED in Oriental regions for centuries and it has been used as an analgesic and a sedative agent. Its constituents, vanillyl alcohol and gastrodin (fig. 6) are known to have
anticonvulsant activity (Yuan et al., 2018). The constituents inhibited glutamate-induced apoptosis in neuronal cells by possessing free radical scavenging and antioxidants protective effect (Yuan et al., 2018). Both antioxidant effects and anti-apoptotic action of these constituents may account in part for the basis of their antiepileptic activities (Yuan et al., 2018).

**Ginseng**
There are seven major species of ginseng, but the most commonly used are *Panax ginseng* (Asian), *Panax quinquefolius* (American) and *Panax japonicus* (Japanese) (Stringer, 2009). The duration of KA-induced seizures in rats were shorter when the animals were pre-treated with a mixture of ginsenosides from Asian ginseng (Stables et al., 2002). Some of the ginsenosides also have been reported to have neuroprotective effects (Stringer, 2009). Ginsenosides (fig. 7) are amphiphilic and have the ability to intercalate into the plasma membrane leading to changes in membrane fluidity (Stringer, 2009), thus altering the function of membrane itself and the functions of receptors and other proteins within the membrane. However, the most accepted theory is the ability of ginsenosides to scavenge free radicals (Stringer, 2009).

**Uncaria rhynchophylla**
In Traditional Chinese Medicine, *Uncaria rhynchophylla* is used to reduce hyper function of the liver, dizziness and epilepsy (Hsieh et al., 1999). Its anticonvulsive effect in KA-induced epileptic seizures in rat has been reported (Tang et al., 2010; Hsieh et al., 1999). The alkaloid components include rhynchophylline, isorynchophylline and isocorynyoxine (fig. 8) were reported to protect neurons from glutamate-induced cell death in cerebellar granule cells (Tang et al., 2010; Shimada et al., 1999). This may be mediated by the inhibition of c-Jun N-terminal kinase phosphorylation and the activity of nuclear factor-κB (Hsieh et al., 1999). *Uncaria rhynchophylla* reduced the firing of hippocampal CA1 neurons by attenuating glial fibrillary acidic protein, S100B protein levels but not GABA_A and transient receptor potential cation channel V-1 receptors (Lin and Hsieh, 2011). Therefore, it is known for its anticonvulsant role through inhibition of abnormal neural discharges and apoptosis (Lin and Hsieh, 2011).

**Pinellia ternata**
Raw *Pinellia ternata* may cause irritation to oral, throat and gastrointestinal mucosa, and may induce vomiting and diarrhea (Marki and Takahashi, 1987). Rhizoma Pinelliae, the tuber of *Pinellia ternata* (Thunb.) Breit. (Araceae), has been widely used as antiemetic, antitussive, sedative and has anti-inflammatory effects (Marki and Takahashi, 1987; Fenglai et al. 2015). Pinellia total alkaloids and Uncaria total alkaloids have synergistic effects in anticonvulsant action when administers together. The mechanism of this activity is related to its ability in reducing excitation of glutamatergic neurons and increasing the inhibition of GABAergic neurons (Cheng et al., 2007).

**Withania somnifera**
*Withania somnifera* (family: Solanaceae, Ayurvedic name: ‘Ashwagandha’) roots are categorised as ‘Rasayanas’, a group of plant-derived drugs reputed to promote health and longevity by augmenting defence against disease, arresting the aging process, revitalising the body in debilitated conditions, increasing the capability of the individual to resist adverse environmental factors and by creating a sense of mental well-being (Weiner and Weiner, 1994). Thirty days’ treatment *Withania somnifera* (fig. 9) root on mice produced a significant decrease in LPO, and an increase in both SOD and CAT, therefore indicating its free radical scavenging ability (Panda and Kar, 1997). Administration of *Withania somnifera* to the mice in the doses of 0.7 and 1.4 g/kg body weight per day for 20 days significantly decreased LPO and increased the activities of SOD and CAT, therefore retaining the normal peroxidative status of the tissues (Chaurasia et al., 2000). *Withania somnifera* also inhibits both the LPO and protein oxidative modification induced by copper (Gupta et al., 2003).

**Magnolia bark**
Another promising source of neurologically active natural plant is the bark of magnolia trees. The isomers magnolol (5,5'-diallyl-2,2'-dihydroxyziphenyl) and honokiol (3,5'-diallyl-4,2'-dihydroxyziphenyl) (fig. 10) are the principal active components of magnolia bark extract, typically making up 1-10% of the dried bark, depending upon the species and the isolation methods (Lee et al., 2011; Patocka et al., 2006). These compounds have been identified as neurologically active agents with anxiolytic, sedative, neuroprotective and anticonvulsant actions in animal models (Chen et al., 2011; Ma et al., 2009; Lin et al., 2005; Kuribara et al., 2000). Magnolol inhibited N-methyl-d-aspartic acid receptor activation (Lin et al., 2005). The inhibitory effects of magnolol on antiepilepsy activity were found to be mediated by the GABA_A/benzodiazepine receptor complex (Chen et al., 2011; Ma et al., 2009).

**Resveratrol-related products**
Resveratrol (fig. 11) is a polyphenol chemical found in a some of plant species, including peanuts, grapes and red wine (Saiko et al., 2008). Based on animal models and cell culture studies, there is some evidences that resveratrol may have potential treatment for diseases ranging from cancer, cardiac disease, and neurodegenerative disorders, although rigorous clinical trial data in humans are sparse (Saiko et al., 2008). A number of biological properties for resveratrol suggest that it could also be beneficial in epilepsy, especially as an antiepileptogenic. Previous studies have indicated that
resveratrol protects against neuronal acute seizures and cell death induced by KA (Wang et al., 2004; Gupta et al., 2002).

Although many plants have been utilized and studied for activity in epilepsy, none of them have yet been developed into a standard medication for the treatment of seizures.

**Challenges in natural products for the treatment of epilepsy**

One of the challenges for the herbal industry is being able to consistently formulate a product, in order to ensure promised pharmacological and clinical results. In other words, chemical standardization is crucial for herbal medicines industry to identify and standardize a particular extract which is responsible for the physiological effect to an acceptable percentage (Cardellina, 2002). Any variation in chemical constituents is attributed to several factors. These include genetic factors (wild and cultivated plants), environmental factors (soil, light, temperature, nutrients, diurnal and seasonal variation), plant organ specificity and manufacturing factors (harvesting, storing, processing and formulating methods) (Khan, 2006). For example ginseng, one potential antiepileptogenic agent, has been found to have significant variation in the composition of ginsenosides (Leung and Wong, 2010; Khan, 2006). Therefore thorough research is necessary to identify these variations.

**Fig. 4: Chemical structures of bioactive constituent isolated from Boerhaavia diffusa.** Boeravinones A (C), Boeravinones B (D), Boeravinones C (E), Boeravinones D (F), Boeravinones E (G) and Boeravinones F (H).

Furthermore, pharmacokinetics of natural product mixtures compounds is also another considerable challenge for the treatment of epilepsy. For example,
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Poor bioavailability issue of curcumin, a potential antiepileptogenic agent, which has low systemic bioavailability following oral administration in both animal models and human (Vareed et al., 2008), and this has restricted its use in the management of human ailments. Poor oral absorption of curcumin might be due to its extremely low aqueous solubility or extensive first pass metabolism and some degree of intestinal metabolism (Shen and Ji, 2012; Vareed et al., 2008). But in view of beneficial therapeutic effects of curcumin, a new formulation in combination with phospholipids was developed to overcome this limitation and this curcumin-phospholipid complex has better oral absorption and bioavailability (Maiti et al., 2007). The same pharmacokinetic issue had been reported in ginseng, in which the ginsenosides are very poorly absorbed after oral administration in vivo with bioavailability of 0.25% to 64.8% (Lu et al., 2009). Poor bioavailability of ginsenosides includes the fact that these compounds may be destroyed in the gastrointestinal tract, metabolized by intestinal microflora and excreted from bile or urine (Lu et al., 2009). Further research to enhance the bioavailability of ginsenosides includes co-administration with adrenaline, emulsification into lipid-based formulation and suppression of the p-glycoprotein efflux system (Leung and Wong, 2010).

Despite generally being regarded as natural and therefore safe by the public, herbal therapies may cause serious-and life-threatening side effects. Long term safety profiles of most herbal therapies are also unknown (Pearl et al., 2005; Ernst, 2003). There are numerous herbal therapies that have been anecdotally reported to cause seizures, including in patients with epilepsy (Luciano and Spinella, 2005). Examples of this effect include gingko nuts (Miwa et al., 2001), essential oils, (Spinella, 2001) evening primrose, *Borago officinalis* (Sirven, 2007) and *Ephedra sinica* (Obach, 2000). As a consequence of these adverse events, the isolation of a pure compound is required. Although many herbal remedies are harmless, numerous products can trigger the central nervous system and could potentially cause or increase the risk of seizures (Tyagi and Delanty, 2003; Spinella, 2001). A recent review of adverse event reports described an association between the use of dietary supplements and seizures (Haller et al., 2005). Furthermore, adulteration, inappropriate formulation, or a lack of understanding of plant and drug interactions have led to adverse reactions that are sometimes life-threatening or lethal. And a proper double blind clinical trial is necessary to determine the safety and efficacy of each plant before they can be recommended for medical use.
In addition, there are herbs and dietary supplements that have the potential to interact with antiepileptic medications via effects and drug-herb interactions, but studies regarding this issue are inadequate (Schacter, 2009). Evidence suggests that St. John’s wart (Obach, 2000), garlic, Echinacea (various Echinacea species), pine bark extract (Pinus pinaster), milk thistle (Silybum species), American hellebore (Veratrum viride), gingko (Kupiec and Raj, 2005; Bressler, 2005), mugwort (Artemisia species) and pipsissewa (Chimaphila umbellata) affect the cytochrome P450 system and may therefore affect serum concentrations of hepatically metabolized AEDs, (Pearl et al., 2005; Luciano and Spinella, 2005; Gil et al., 2002; Johanns et al., 2002) possibly with fatal consequences (Kupiec and Raj, 2005).

**CONCLUSION**

Currently, there is no comprehensive theoretical model to account for the rationale of natural product use in epilepsy. Previous studies have suggested that people who used natural products were different from non-users in socio-demographic and health characteristics, including gender, age, race, education level, and income (Kim et al., 2006; Wilson et al., 2006; Astin, 1998). Moreover, dissatisfaction with the cost and effectiveness of conventional therapies (Murray and Rubel, 1992; Gross-Tsur et al., 2003; Jean and Cyr, 2007), the need for personal control over healthcare decisions (Duggan, 1995) and the compatibility of natural products with individual values, or spiritual or religious philosophy or beliefs (Johanns et al., 2002) play important roles in decisions to seek out alternative therapies.

A widely recognized goal of epilepsy drug research is the identification of disease-modifying or antiepileptogenic drugs that can inhibit the progression of epilepsy or completely prevent its development in the first place (Loscher and Schmidt, 2006). Natural products may retard epileptogenesis and could be potentially be developed as antiepileptogenic drugs in acquired brain injury. However, a number of steps must be taken before the findings can be translated from animal models to human studies. Thus, specific mechanisms of the neuroprotective, or antiepileptogenic capability of the compounds needs to be fully understood.

Herbal medicines and their constituents that have been shown experimentally to act against epilepsy should be further evaluated in molecular and animal models and moved into clinical development to assess their efficacy, safety and tolerability. Therefore, natural products may potentially be developed as new treatment options for patients whose seizures are uncontrolled despite available AEDs.

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