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REVIEW ARTICLE

Recent Advances in Antiepileptic Herbal Medicine

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ARTICLE HISTORY

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Abstract: ***Background*:** Epilepsy is one of the most common neurological disorders worldwide, with about 80 percent of cases thought to be in developing nations where it is mostly linked to superstition. The limited supply, high cost as well as low efficacy and adverse side effects of antiepileptic drugs (AEDs) is a matter of major concern. Herbal medicine has always been traditionally part of treatment of epilepsy. Herbal medicines are generally well tolerated, with fewer side effects.

***Method*:** To highlight some herbal extracts that have been studied for their anticonvulsant activity in animal models, literature search from PubMed and Science Direct, was performed. The keywords for the search consisted of combinations of the following terms: Herbal antiepileptic and/or anticonvulsant, botanicals + epilepsy. Literature published in the last five years was considered.

***Results*:** Eighteen (18) anticonvulsant herbal agents are reported and discussed. Experiments mostly consisted of phenotypic screens in rodents, with little diversity in screening methods. In most experiments, the tested extracts prolonged the time to onset of seizures and decreased their duration. Most experimenters implicate potentiation of GABAergic activity as the mode of action of the extracts, even though some experimenters did not fully characterise the bioactive chemical composition of their extracts.

***Conclusion*:** Potential herbal remedies have shown positive results in animal models. It remains unclear how many make it into clinical trials and eventually making part of the AED list. More rigorous research, applying strict research methodology with uniform herbal combinations, as well as clinical studies are urgently needed.

Keywords: Neuron, drug, epilepsy, herbal medicine, GABA, brain.

1. INTRODUCTION

Epilepsy is one of the most common chronic neurological symptom of diseases, affecting around 60 million people worldwide [1, 2] and affects people of all ages [3] with a higher prevalence in developing countries where it is linked to witchcraft as divine punishment [1]. Epilepsy is defined as recurrent unprovoked seizures generated from excessive and abnormal cortical neuronal activity in the brain. An episode of epilepsy is characterized by a convulsive or non-convulsive seizure [4, 5]. In pediatric population, it is very often associated with cognitive, behavioral and psychiatric comorbidities [6]. Most of the cases of epilepsy are idiopathic though some cases result from brain injury, stroke, brain tumor, severe malaria and drug abuse. Certain genetic mutations have also been implicated as causes of some cases of epilepsy [1, 7].

Most Antiepileptic drugs (AEDs) do not prevent or reverse the pathological process that underlies epilepsy, hence the continuing search for new therapies with fewer side effects and better efficacy [8]. Moreover, 30–40% of patients typically develop pharmacoresistant or intractable epilepsy [2]. In most cases, traditional healers are often the first line of contact in the search of therapy because of its link to supernatural powers [9], unavailability and high cost of conventional AEDs in developing countries [1]. Herbal medicine plays a very important role in meeting the primary health care needs of the population, with Africa and Asia being the continents with most of the users [10]. Some medicinal plants have shown potential as new, safe treatment options [11, 12]. Although many of them have traditionally been used as sedative and antiepileptic agent, there is still lack of controlled experimental reports on therapeutic use [13]. Stringer [14] states that more than 50 plants have shown some anticonvulsant activity whereas Xiao *et al*. [15] noted that 23 botanicals were used in Chinese traditional medicine to treat epilepsy but none of them has been developed into a standard medication for the treatment of seizures.

The therapeutic potential of herbal plants and some of their bioactive compounds have been the subject of extensive research. As with any other drug discovery, the process involves a screening step in animal models. The aim of this

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Table 1. Effects of herbal extracts tested for anticonvulsant activity in animal models.

Herb	Experimental Model	Effect/Results	Refs.
Uncaria rhynchophylla	Lithium-pilocarpine-induced status epilepticus in Sprague-Dawley rats	Pretreatment with rynchophilline prior to seizure induction significantly reduced the percentage of animals that built up to seizure epilepticus compared to the sham control group. In addition, the latency to both convulsive and non-convulsive seizure was significantly increased while the seizure score was reduced.	[16]
Cannabis (Cannabinoid compound)	Mouse PTZ-induced clonic seizure.	ACEA administered i.p (10 mg/kg) with PMSF (30 mg/kg) significantly enhanced the anticonvulsant activity of ethosuximide, phenobarbital, and valproate but not clonazepam. This treatment also increased the free plasma and total brain concentration of ethosuximide and valproate, but not clonazepam and phenobarbital.	[6, 17]
Desmodium triflorum	Swiss albino PTZ-induced clonic seizure mice	Pretreatment with AEDT (400 or 800 mg/kg p.o) showed significant delay in the onset of convulsion and duration of the seizures compared to the control treated mice. Moreover, the maximum studied dose of 2000mg/kg was found to be nontoxic in oral toxicity studies. Importantly, no mortality was recorded.	[18]
Viscum album	Swiss albino mice and Wister albino rats of either sex in the PTZ- induced seizure model.	Pretreatment with the extract reduced the phases of the various epileptic seizures and increased the latency to the first convulsion. The extract also reduced the locomotor activity, as does other AEDs, though less than diazepam.	[19]
Morus alba	Isonicotinic hydrazide (INH) and maximal electroshock (MES) in Wister albino rats	Isolated morusin injection (i.p) ameliorated the epileptic seizure. It increased the latency to onset of seizure and decreased the duration of convulsions, with no mortality was recorded. At 5 mg/kg and 10 mg/kg dose, Morusin exhibited significant reduction and total absence in tonic hind limb extension (THLE) respectively	[20]
Berberis integerrima	PTZ-induced seizures in mice	Hydromethanolic and chloroform fractions of the extract increased the onset time of HLTEs compared to the negative control group. However, the extracts did not show any positive effect on reduction of HLTE duration, indicating absence of protective effect on protective activity against grand mal epilepsy. Moreover, it did not show significant protection against mortality.	[21]
Mussaenda philippica	MES, Picrotoxin, PTZ and Strychnine-induced seizures in Swiss albino mice and Wister rats of either sex.	Hydroalcoholic extracts at 100-200 mg/kg enhanced the anticonvulsant effects of other AEDs and may help to control grandmal and petitmal epilepsy. The extract produced no mortality up to 2000 mg/kg.	[22]
Justicia pectoralis	Female Swiss mice pilocarpine induced seizure	Pretreatment with standardized extract of *Justicia pectoralis* increase latency to the first seizure and latency for death.	[23]
Gladiolus dalenii	MES and PTZ induced seizures in mice	When co administered at a dose of 30mg/kg with diazepam at a dose of 0.05mg/kg, the two produced additive effects. The extract increased the level of cerebral GABA in a concentration-dependent manner.	[24]
Ficus. religiosa	PTZ-induced seizures in mice	Co-administration of the ethyl acetate fraction of *Ficus* along with a sub effective dose of phenytoin (15mg/kg) suppress seizures.	[25]
Withania somnifera	Pilocarpine induced epilepsy in male Wister rats	All animals injected with pilocarpine developed status epilepticus within 20 to 40 minutes. Treatment using *Withania somnifera* extract and Withanolide A significantly reversed the increased cerebellum glutamate content associated with epilepsy, well comparable to the effect of carbamazepine.	[26]
Lobelia nicotianaefolia	PTZ induced seizure model in mice	Pretreatment with isolated lobeline at 10, 20 and 30 mg/kg significantly delayed onset and the duration of clonic and tonic seizures compared to the vehicle administered control. 20mg/kg provided the highest protection against mortality. GABA level was found to be dose dependently increased up to dose of 20 mg/kg but not at 30mg/kg, corresponding to the observed effect in seizure amelioration	[27]

(Table 1) contd….

Herb	Experimental Model	Effect/Results	Refs.
Marsilea quadrifolia	PTZ induced seizure model in rats	Pretreatment with the water extract (MQ WE) at the dose of 200 and 400 mg/kg or ethanol extract (MQ EE) at the dose of 100, 200 and 400 mg/kg, exhibited significant increased latency to seizure comparable to diazepam. The seizure severity score and duration of epileptic seizure was decreased significantly. In addition MQ EE, MQ WE and diazepam decreased or partially blocked the epileptiform activity induced by PTZ as seen in EEG tracing.	[13]
Passiflora incarnata	Subconvulsive doses of PTZ (50 mg/kg; *i.p.*) at an interval of 5 days for 15 days in Male Albino Swiss mice	Treatment with the extract significantly decreased the seizure severity score in a dose dependent manner, with complete abolishment of seizure at a dose of 300 and 600 mg/kg on the 15th and 10th days, respectively, similar to the effect of diazepam.	[28]
Mondia whitei	Pilocarpine induced seizure	Methanol extract, ethyl acetate and hexane fractions at 25, 50 and 100mg/kg exhibited delayed seizure onset and reduced the duration in a dose dependent manner. Although it did not prevent the seizures, it protected the rats from mortality and exhibited partial recovery	[29]
Gastrodia elata	Penicilin cocaine induced seizure	A combination of gastrodin and phenytoin has synergistic anticonvulsive and neuroprotective effects in mice.	[30, 31]
Phytol	adult male Swiss mice of pilocarpine induced seizure model	Mice that had received phytol injection pre pilocarpine injection survived. The protection against seizure and the increase in latency to status epilepticus was dose dependent. Moreover, intraperitoneal injection of phytol did not show any toxic effects.	[32]

review is to highlight recent advances in the search for herbal therapy against epilepsy. The review is restricted to animal studies that have been published in the last five years. This review also points the reader to other review works that have been done by others within this period.

2. METHOD

To prepare this review, a literature search from PubMed and Science Direct, was performed. The keywords for the search consisted of combinations of the following terms: Herbal antiepileptic and/or anticonvulsant, botanicals + epilepsy, limiting the search results to the last five years.

3. RESULTS

Elsewhere, Sahranavard *et al*. reviewed medicinal antiepileptic plants used in Iran and listed 11 such herbal remedies [33]. Sriranjini *et al*., reviewed some antiepileptic botanicals used with respect to ayurverda [8] while Tagarelli *et al*. summarized 12 herbal remedies used in Italy [34].

4. DISCUSSION

Herbal medicines generally have a broad spectrum because they are an assortment of bioactive compounds. It is worth noting that most of the extracts tested were chosen based on knowledge that they are traditionally used against other ailments or as antiepileptics by traditional herbalists. Although herbs have been used for years and tested in animal trials, there is a lack of standardization and safety and efficacy studies, restricting their utilization in modern medicine [35].

For a substance to be an effective anticonvulsant, it must cross the blood-brain barrier. Selecting the appropriate model is a key factor in AED screening in the case of false-positive or false-negative results [36] as different models could simulate dissimilar kinds of epilepsy. The processes underlying epileptogenesis differ among models [37]. Maximal electroshock (MES) and subcutaneous pentylenetetrazol (PTZ) are the two most widely used models in screening compounds for antiepileptic activity. Other less commonly used models exist, each modelling a particular form of epilepsy. Positive results in either model suggest that the test compound, or its metabolite crossed the blood–brain barrier and exerted its effect in the central nervous system [1]. In this review, all experiments consisted initially of phenotypic screens in rodents using predominantly PTZ [6, 13, 18, 19, 21, 22, 24, 25, 27, 28], MES [20, 22, 24] and pilocarpine [16, 23, 26, 32] seizure models. A few researchers dared to test their extracts in more than one phenotypic screening models [13, 20, 22, 24]. There is considerable concern among AED researchers that the limited models being used only identify me-too drugs that act by the same old physiological mechanisms, thus limiting chances of discovering novel therapies with different targets [38, 39], especially compounds with efficacy against drug-resistant seizures. Novel potential targets for the treatment of epilepsy have been described [1]. Time is more ripe now than never before for the diversification and adoption of more screening animal models. Besides, testing a substance in different models gives a more holistic idea of the substance's efficacy as each model models a different form of epilepsy and thus a different mechanism of action of the test extract.

It is evident that herbal extracts have potential to be a rich source for safer and more effective, low-cost and culturally acceptable antiepileptic agents especially in resource-poor regions. In most experiments, the tested extracts pro-

longed the time to onset of seizures and decreased their duration. The mode of administration was either intraperitoneal or oral, and where it was recorded, the toxicity was non-lethal up to a dosage of 2000mg/kg. Most importantly, some extracts were able to completely prevent the experimentally induced seizures at non-lethal doses [20, 28] or from death caused by induced seizure [18, 20, 22, 29] while others worked only in combination, as adjuvants, offering additive or synergistic effects with conventional AEDs. This is an important aspect to bear in mind as it holds the potential to reduce the dosage of the conventional AEDs when used in combination with herbal extracts. This would in turn reduce the current problem of side effects caused by conventional AEDs.

The two most important neurotransmitters involved in the regulation of brain neuronal activity are the excitatory neurotransmitter glutamate and the inhibitory neurotransmitter GABA. The most widely understood mechanism of action of AEDs include modulation of voltage-gated cation channels, potentiation of GABA-ergic activity and inhibition of glutamatergic processes. Substances that are effective against PTZ induced seizures are thought to act on GABA transmission while those effective against the MES model are considered to block sodium channels. Majority of experimenters have focused on substances whose mode of action involve these neurotransmitters, particularly the inhibition of enzymes involved in the degradation of GABA, as seen from the wide use of PTZ seizure induced model [30]. This is probably because of the ease of accessibility and implementation the PTZ rodent model. Herbal extract either interact with GABA receptors or have anxiolytic and sedative properties, although other pharmacological mechanisms, *i.e.*, neuroprotective activity, might be involved [33]. Indeed from this review, most experimenters implicate potentiation of GABA-ergic activity as the mode of action of their extracts [18-20, 24, 27, 30]. Others notably implicate the cholinergic system [23], antioxidants [25] and AMPA receptors [26]. As earlier stated, the limited range of models used limit to discovery to only me-too drugs.

A lot of plants have shown some anticonvulsant activity, but to date, not many have been incorporated into standard medication for the treatment of epilepsy, while the disease burden persists [14]. So, what is the impediment in rationalizing the use of plant extracts and plant-derived compounds for the treatment of seizures and epilepsy? Of note, only a small number of experimenters fully characterized the bioactive chemical composition of their extracts. Where they have been characterized, a limited number of studies have been performed in order to assess the rate of absorption of these compounds. Also, not all researchers bother to carry out toxicity tests of their extracts. It is the author's considered view that the initial screening process should be more rigorous and inclusive. The area of herbal remedies hold the future for a safe alternative to the current synthetic drugs. The least that should happen is that herbal products should be incorporated as adjuvants to the conventional AEDs.

CONCLUSION

The limited efficacy of AEDs is still a matter of concern. Animal models have been used since time immemorial to test new drugs, and are continually becoming more sophisticated as technology and scientific understanding progresses. This review has presented some of the potential herbal remedies that have been tested and shown positive results in animal models. It remains unclear how many of such potential remedies actually make it into clinical trials and eventually making part of the AED list. More research in this area, applying strict research methodology with uniform herbal combinations, as well as clinical studies with selected standardized botanical extracts are urgently needed to determine which is most efficacious [1, 11]. As Sucher and Carles [1] put it, "it is to the detriment of patients and progress if drug development efforts ignore the potential of plant-derived compounds". Rigorous pre-clinical and clinical studies are encouraged to help the legacy of herbal medicine gain more impact and recognition.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The author declares no conflict of interest, financial or otherwise.

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