

Herbal extracts: the future treatment option for drug-resistant epilepsy

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Abstract

Epilepsy is a neurological disorder characterised by two or more unprovoked seizures. The high prevalence and incidence of epilepsy globally, especially in Asia, has remained a big concern over the course of centuries. Patients are usually prescribed the already known anti-epileptic drugs, but even after going through three different generations of anti-epileptic drugs, some people still suffer from drug-resistant form of epilepsy. These patients are usually prescribed a higher dose of anti-epileptic drugs, which results in more adverse effects. That is why new treatment options, like herbal extracts, should be explored for patients who do not respond to the classic anti-epileptic drugs. The current narrative review was planned to explore if herbal extracts can be the future for the treatment of drug-resistant epilepsy.

Keywords: Epilepsy, Herbal extracts, Drug-resistant epilepsy, Anti-epileptic drugs.

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Introduction

Epilepsy is known as a chronic disease of the brain and is characterised by occurrence of two or more unprovoked seizures. There can be several causes of seizures, which are categorised into structural, genetic, infectious, metabolic, immune, and unknown types¹. Epilepsy can have neurobiological, cognitive, psychological, and social consequences². Following stroke and neurodegenerative diseases, epilepsy is known as the third most common neurological disease in elderly population³. Anti-seizure drugs are used as the first line of treatment to control the seizures. Despite the availability of various drugs, one-third of the patients remain refractory to seizures⁴. The current review, as part of an ongoing research to discover novel drugs and treatment options for such patients, was planned to discuss how herbal treatments can be used for successful treatment of epilepsy with minimum side effects.

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Epilepsy and prevalence of epilepsy in Asian countries

Epilepsy is a chronic non-communicable disease of the brain that affects around 70 million people worldwide⁵. The global incidence and prevalence of epilepsy is 50 in 100,000 and 700 in 100,000, respectively. Approximately 4 billion people (50% of the global population) are part of Asia, and, among them, 23 million people have epilepsy⁶. The overall prevalence of epilepsy in Pakistan is estimated to be 9.99 per 1,000 population⁷. The highest prevalence is in people aged <30 years and there is a slight decrease in prevalence in those aged 40-59 years⁷. A recent review in India showed that among a total of 17,91,541 participants, 5,890 were diagnosed with epilepsy, and the pooled prevalence was 4.7 per 1,000 population⁸. Another population-based door-to-door survey across Malaysia showed that the prevalence of lifetime epilepsy was 7.8 per 1,000 population⁹. Overall prevalence of epilepsy in Laos was estimated to be 7.7 cases per 1,000 inhabitants¹⁰. Nepal also has a high prevalence, estimated to be around 7.3 per 1,000 population, with a treatment gap of over 80%¹¹. The prevalence rate of epilepsy in Thailand was 7.2 per 1,000 population¹². In China, the prevalence rate was reported to be ranging from 0.9 to 8.5 per 1,000, mostly because of cerebrovascular diseases¹³. It is clear that epilepsy is a genuine concern in Asia, and steps need to be taken to find out novel solutions to provide a better life to epilepsy patients.

Treatment according to the aetiology of epilepsy

Typical treatments are used to treat 6 different types of epilepsy, according to aetiology, as approved by the International League Against Epilepsy (ILAE) (Table 1)¹.

Drug-resistant epilepsy

Drug resistant epilepsy (DRE) is defined as the persistence of seizures despite at least two syndrome-adapted anti-seizure drugs (ASDs) used at an efficacious daily dose. Seizures are not completely controlled in these patients even after taking ASDs singly or even in different prescribed combinations⁴. Clinical evidence shows that if two ASDs are ineffective in a patient, the administration of additional ASDs is not likely to be effective¹⁴. Such pharmaco-resistance leads to reducing the quality of life of these patients and can enhance mortality and

Table 1: Typical options to treat 6 different types of epilepsy.

Type Of Epilepsy	Typical Treatment
Structural	1.Begin with anti-epileptic drugs 2.If resistance to anti-epileptic drugs exists, then resective surgery should be considered
Genetics	1.Genetic diagnosis to find out the gene defect 2.Individualized (precision) treatment
Infectious	1.Identifying the cause of inflammation 2.Treatment of the infection and corresponding predisposing factors 3.Specific anti-inflammatory drugs
Metabolic	1.Drugs like levetiracetam and benzodiazepines which are known as the broad-spectrum anti-seizure medication are a better initial choice 2.For drug refractory seizures, trial of pyridoxine, biotin, and folic acid is recommended 3.Supportive care and prevention of catabolism should be initiated when no other treatments are available
Immune	1.Immunosuppression usually with steroids, plasma exchange and/or intravenous immunoglobulin 2.T cell function targeting therapies can also be used, like, tacrolimus and natalizumab
Unknown	1.Try to find out the cause 2.Treat with anti-epileptic drugs 3.If doesn't respond, see the effects of drugs with new targets

GABA: Gamma-aminobutyric acid. TREK-2: TWIK-related K⁺ channel-2, NMDA: N-methyl-D-aspartate.

morbidity.

Anti-epileptic drugs

Anti-epileptic drugs (AEDs) have been the main pillar of epileptic treatment for a long time. Until 1993, there were only a few AED choices available. However, up to 17 new approved anti-epileptic drugs are currently available in the market. Yet, the target of these drugs are only the symptoms, and they fail to cure the cause of seizures. Currently available medications work on ion channels, receptors, transporters, and enzymes to restore the balance between the inhibitory and excitatory neurotransmitters¹⁵. Although now there are numerous drugs available, almost 50% of the patients do not respond to the first AED prescribed to them, and one-third remain resistant regardless of any addition to the treatment options. It is a known fact that some AEDs are effective in certain seizure types, and that is why knowing the seizure type is of utmost importance before prescribing any AED¹⁶.

The final decision of treatment is based on the evaluation of the balance between the expected efficacy and the

safety profile of the available AEDs. Clinicians usually make their choices according to the mechanism of action of AEDs, especially in patients who are prescribed with polytherapy¹⁷. Some of the common allopathic drugs used in epilepsy are carbamazepine, clonazepam, diazepam, ethosuximide, felbamate, gabapentin, lamotrigine, midazolam, phenobarbital, phenytoin, primidone, topiramate, valproic acid and vigabatrin¹⁸. These drugs have different mechanism of actions and are used to treat different types of seizure. For example, phenytoin, which is one of the oldest used AEDs, is mainly used for treating partial and tonic-clonic seizures¹⁹, while levetiracetam (LEV) is usually valuable against generalised and partial seizures²⁰.

The mechanism of action of four main classes of AEDs has been established: modulation of voltage-gated ion channels; enhancement of gamma-aminobutyric acid (GABA)-mediated inhibitory neurotransmission; attenuation of glutamate-mediated excitatory neurotransmission; and modulation of neurotransmitter release via a presynaptic action²¹.

AEDs are usually classified as older or first-generation, or newer or second- and third-generation drugs²². First generation of AEDs include valproic acid, benzodiazepine, phenobarbital, primidone, carbamazepine, phenytoin and ethosuximide²³. The second generation comprises lamotrigine, levetiracetam, topiramate, zonisamide, felbamate, gabapentin, oxcarbazepine, rufinamide and pregabalin. The third-generation AEDs approved in the last few years are lacosamide, eslicarbazepine acetate, perampanel, brivaracetam and cenobamate²⁴. There are several steps taken to treat an epileptic patient (Figure 1).

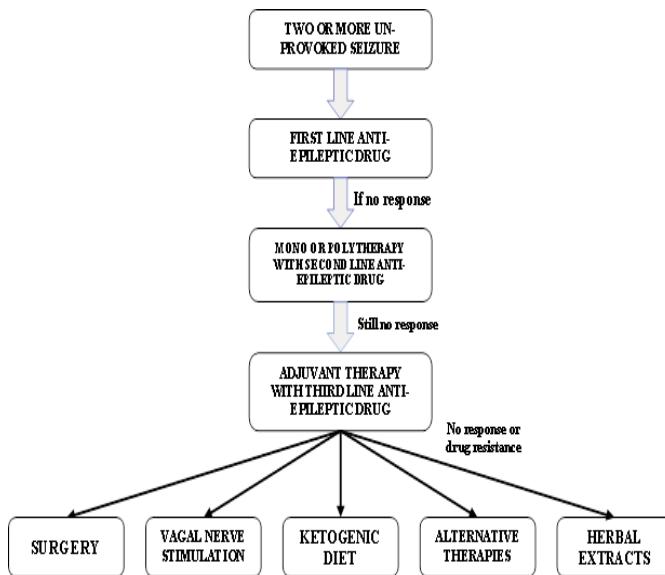


Figure-1: Series of steps taken to treat an epileptic patient.

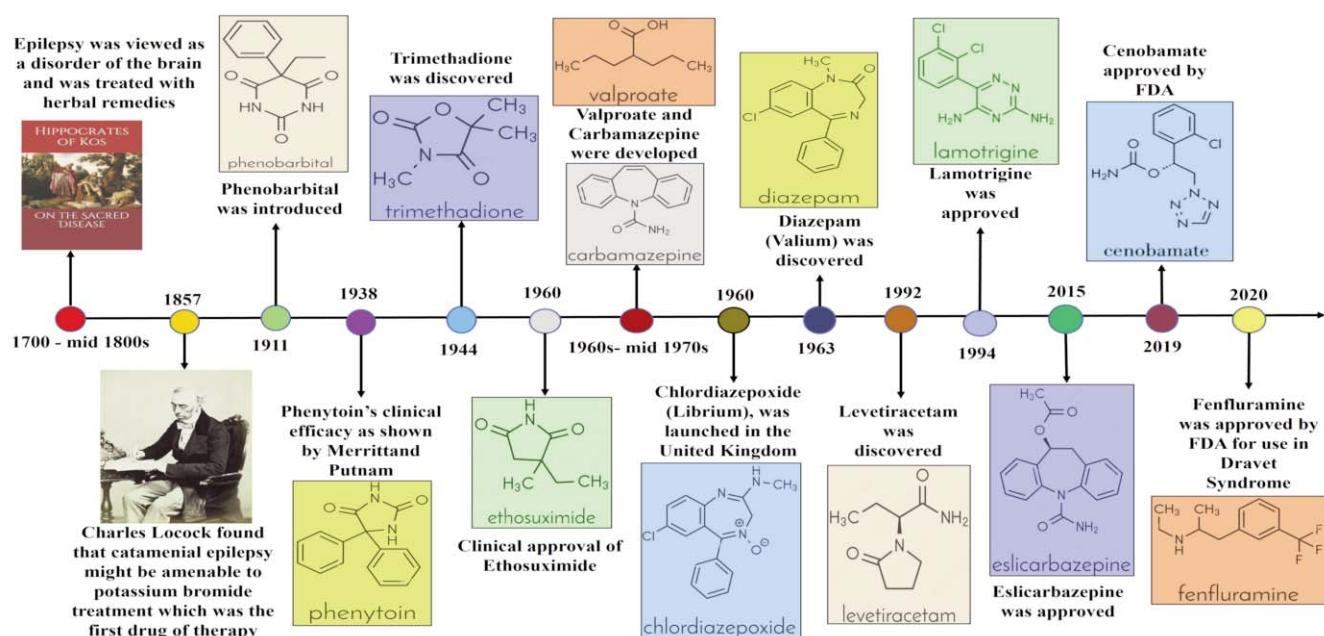


Figure-2: A brief history of some of the anti-epileptic drugs from the early 18th century till 2020.²⁵⁻³⁰

Potassium bromide was the first drug for epilepsy, followed by the discovery of phenobarbital, phenytoin, trimethadione, ethosuximide, valproate and carbamazepine. Clordiazepoxide was the first available benzodiazepine, followed by diazepam^{2]} and the process is continuing to date²⁵⁻³⁰ (Figure 2).

There are numerous options in the market for single or adjuvant therapy, but the administration of these drugs over a long period of time and in higher doses can result in complications, including endocrine, metabolic, and psychiatric disorders, and drug interactions and idiosyncratic reactions in a few cases. The most common side effects of AEDs include dizziness, nausea, and headache. Further adverse effects, such as skin, visual and auditory problems, kidney disorders, liver dysfunction and pancreatitis, have also been reported³¹. Patients suffering from drug resistance are prescribed with high dose of these AEDs which results in higher chances of side effects. Additionally, the incidence of sudden unexpected death in epilepsy patients (SUDEP) is greater in the drug-resistant form of epilepsy⁴.

AEDs are now the most common and the most effective treatment option for epileptic patients, among which about 15% spend approximately 2-5 years to find an AED regimen which effectively treats their symptoms, and another 25-30% are resistant to any kind of AEDs and need to be moved towards other treatment options, like vagal nerve stimulation or surgery.

Herbal extracts: a potential treatment for epilepsy

Herbal extracts are emerging as an effective treatment option for patients who do not respond to AEDs. Research on discovering the mechanism of action of anti-convulsant herbal extracts is ongoing. Examples of herbal medications are *zingiber officinale*, *pimpinella anisum*, *carum carvi*, *moringa oleifera*, *lavandula officinalis* and *gastrodia elata blume* (Table 2).

Table-2: Type of animal models used to study the anti-convulsant properties of herbs till date.

Herbal Extracts	Animal Model
<i>Zingiber officinale Rosc.</i>	Pentylenetetrazol (PTZ) model (Pro-convulsant model)
<i>Pimpinella anisum L.</i>	Pentylenetetrazol (PTZ) model (Pro-convulsant model) and Maximal electroshock (MES)
<i>Carum carvi L.</i>	Pentylenetetrazol (PTZ) model (Pro-convulsant model)
<i>Moringa oleifera Lam</i>	Pentylenetetrazol (PTZ) model (Pro-convulsant model), Picrotoxin-induced convulsion and, Strychnine-induced convulsion
<i>Lavandula officinalis</i>	PTZ-kindling model
<i>Gastrodia elata</i>	Kainic acid induced epilepsy, Pentylenetetrazol (PTZ) model (Pro-convulsant model) and Maximal electroshock (MES) and Lithium pilocarpine model of epilepsy

Herbal extracts are known to be more effective, low-cost, safer agent to treat epilepsy, and it is a culturally acceptable treatment option for people living in resource-poor regions³². Previously, it was discovered that few extracts are completely able to prevent the induced seizures at a non-lethal dose and some also worked in combination, showing a synergistic or additive effects with conventional AEDs³². Conventional anti-epileptic drugs are known to have inevitable and undesirable side effects with increasing dosage, but traditional herbal extracts are safer to use and result in better patient compliance³³.

Some herbal extracts and their benefits

Zingiber officinale Rosc. (Zingiberaceae), which is also known as ginger, is a perennial and herbaceous plant with a long cultivation history. Ginger rhizome is known to be prescribed traditionally as a Chinese herbal medicine³⁴. It has numerous benefits, such as antioxidant, anti-inflammatory, anti-microbial, anti-cancer, anti-obesity, anti-diabetic, anti-nausea, anti-emetic, anti-allergic, neuroprotective, hepatoprotective, cardiovascular protective, and respiratory protective activities³⁴. It has known anti-convulsant effect, which has been proven on pentylenetetrazol (PTZ) model (pro-convulsant model) on rodents and larval zebra fish.

Anise (*pimpinella anisum* L.) belongs to the apiaceae family and is known to be one of the oldest and commonly used spice plants³⁵. It has a variety of properties, such as diuretic, anti-hypertensive, anti-diabetic, anti-cancer, anti-microbial, analgesic, anti-inflammatory, antioxidant, anti-fungal, anti-viral, muscle relaxant, anti-stress, and, most importantly, neuroprotective, and anti-convulsant effects³⁶.

Carum carvi L., which also belongs to the apiaceae family, is one of the most used medicinal plants in conventional medicine³⁷. Pharmacological potencies of caraway seeds include anti-microbial, analgesic, anti-inflammatory, anti-anxiety, anti-hyperglycemic, and anti-spasmodic properties, and it has also been used to treat dyspepsia, flatulent indigestion, diarrhoea, and hysteria³⁸. Studies have shown that it also has anti-convulsant effects³⁸.

Pimpinella anisum L and *Carum carvi* L are considered to be safe and are well-tolerated, but they do have an allergic potential³⁹.

Moringa oleifera Lam. which is native to India and is cultivated across the world, is used in traditional phytomedicine and as a rich source of essential nutrients. Its leaves are known to be rich in flavonoids, carotenoids, and ascorbic acid. It has numerous important properties,

such as antioxidant, anti-inflammatory, anti-diabetic, anti-cancer, cardioprotective, hypocholesterolemic, hepatoprotective and anti-asthmatic⁴⁰. Also, it is known to be useful in the treatment of neuro-dysfunctional diseases, such as epilepsy, ischemic stroke, and Alzheimer's disease. It has been shown to have anti-convulsant and neuroprotective effect⁴¹. It is reported that a dose of 14g dried leaf powder daily does not have any side effects⁴².

Lavandula officinalis (lamiaceae), commonly known as ustu khuddoos, or lavandula, has been used in Iranian traditional medicine for treating nervous disorders like dementia and epilepsy for a long time. Some studies have shown that it has anticonvulsant effects on chemically-induced seizures in animal models. Its mechanism of action includes inhibiting the release of glutamate, enhancing the effects of GABA receptors, blocking the calcium channels, and producing anti-oxidant effect⁴³.

Gastrodia elata Blume (G. elata) herbal plant has been used for numerous conditions, including dizziness, headache, stroke, epilepsy, spasm, amnesia, and others, for centuries. Several studies have demonstrated that the active compounds of *Gastrodia elata*, p hydroxymethylphenyl-β-D-glucopyranoside (gastrodin) and 4-hydroxybenzyl alcohol (HBA) can improve neurological disorders by crossing the blood-brain barrier⁴⁴.

Some herbal extracts have a known mechanism of action (Table 3)⁴⁵.

Table-3: Mechanism of action of a few bioactive components of herbal extracts⁴⁵

Canabidiol	GABA receptor agonist-inhibitor of voltage dependent sodium channels, and T-type calcium channels
Flavonoids	GABA receptor agonist-activator of voltage gated potassium channels- inhibitor of L-type calcium channels- inhibitor of glutamate release activator of the TREK-2 two pore domain potassium channels
Alkaloids	At low concentration it stimulates the sodium, potassium, and ATPase activity, it increases the gradient of sodium across the cell membrane, which can result in enhancing the Na ⁺ -Ca ²⁺ exchanger activity, leading to Ca ²⁺ outflow
Monoterpenoids	TRPA1 channel inhibitor-activator of GABA receptor-inhibitor of voltage gated sodium channels-increase the Ca ²⁺ activated K ⁺ current-GABA receptors agonist- inhibitor of L-type calcium channel
Saponins	Glycinergic and GABAergic-inhibitor of NMDA receptors- antagonists of calcium channels

Future possibilities for treatment of epilepsy

As discussed, one-third of epileptic patients suffer from drug-resistant epilepsy despite receiving higher dose of several anti-epileptics, which results in various side effects⁴⁶. One animal model which can serve as an excellent model for ongoing research is the rodent model of treatment-resistant epilepsy⁴⁷. Researchers are now moving towards the lithium pilocarpine model and some herbs, like *gastrodia elata*, are already being investigated. To further prove the efficacy of these herbs as an anti-convulsant, more research needs to be conducted, especially using the lithium pilocarpine model of epilepsy.

Limitations: Among the herbal extracts that are known to have an anti-convulsant effect, majority of them have been tested on a convulsant or seizure model, or if tested on a true seizure model, they were administered before inducing the seizure. Another problem faced is that the mechanism of action and the active constituents of majority of these herbal extracts are also not known yet.

Conclusion

More research is required to prove the efficacy of herbal extracts on a true model of drug-resistant epilepsy, and to discover their active constituents plus mechanism of action responsible for their effects. This might lead to a new treatment option for patients suffering from drug resistance and to improve the quality of their day-to-day life.

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