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Mechanistic Role of Herbals as Alternative Therapy for Epilepsy

Diksha Sharma, Veerta Sharma, Gaaminepreet Singh, Thakur Gurjeet Singh and Amarjot Kaur Grewal*

Chitkara College of Pharmacy, Chitkara University, Punjab-140401, India

*amarjot.kaur@chitkara.edu.in (Corresponding Author)

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ABSTRACT

Botanicals and herbs have been used by people with epilepsy for ages in various cultures across the world. Patients in both developing and developed nations are currently using herbal remedies to manage seizures or side effects from antiepileptic medicines (AEDs). The deleterious effects of AED medication have a greater impact on the patient's life than seizures. Alternative remedies should be used to treat and manage epilepsy because synthetic pharmaceuticals have risks. Epilepsy may be managed and treated using herbal medicines that have fewer negative effects than pharmaceutical medications. Therefore, the current review discusses about the herbal drugs used in treatment of epilepsy.

Abbreviations

5-HT2C: 5-hydroxy-tryptamine2C
AChE: Acetyl-cholinesterase
AEDs: Antiepileptic drugs
BM: Bacopa monnieri
CBD: Cannabidiol
DMY: Desmethoxyyangonin
EEG: Electrographic seizure
GABA: Gamma-aminobutyric acid
Glu: Glutamate
MES: The maximal electroshock seizure
mTOR: Mammalian target of rapamycin
NMDA: N-methyl-D-aspartate receptor-1
NTs: Neurotransmitters
PTZ: Pentylenetetrazol Induced Seizure
TPM: Topiramate

1. Introduction

Epilepsy is the most frequent neurological illness that harms one's quality of life and causes health problems. It affects around 70 million people approx. in the world (Kaur et al., 2016). Recurrent unprovoked seizures caused by excessive and abnormal cortical neuronal activity in the brain are referred to as epilepsy. A convulsive or non-convulsive seizure is the hallmark of an epileptic episode (Manchishi et al., 2018). Seizures in children are most commonly caused by genetics, perinatal traumas, and cortical development abnormalities. In adults and in elderly people encephalitis/meningitis, traumatic brain injury, and brain tumors are the most prevalent causes of seizures (Falco-Walter et al., 2020). Most seizures can be controlled with antiepileptic drugs (AEDs) and surgery to remove the epileptogenic lesion.

The current antiepileptic drug therapy for epilepsy has dose-related side effects, chronic toxicity and teratogenic effects. Around thirty percent of patients continue to have seizures despite current antiepileptic drug therapy(Asif et al., 2014). The world health organization advises using herbal medication of proven safety and efficacy in healthcare programs in developing countries (Amos et al., 2001).Ongoing research has attracted a lot of attention worldwide. On the other hand, nature is rich in biological and chemical diversity. Several plants have been used in traditional medicine remedies and some are also used to treat epilepsy. Herbal medicines are widely used globally due to their broad applicability and therapeutic efficacy with few adverse effects (Asif et al., 2014). In this review we discussed the several medicinal plants having anticonvulsant properties

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2. Epilepsy Types

Epilepsies are divided into generalized and localized epilepsies based on the seizure in the brain. Generalized epilepsies begin with aberrant brain activity involving both hemispheres, whereas focal epilepsies begin with seizures that originate locally (that may spread)(Scheffer et al.,2018). It is essential to diagnose the particular type of epilepsy before prescribing the AED medication.The choice of AED is based on the type of epilepsy that affects the part of a person's brain. Myoclonic seizures, tonic/atonic / clonic / absence seizures are all caused in people who have generalized epilepsy. Individuals with focal epilepsy may experience focal seizures, impaired awareness seizures and focal motor & nonmotor seizures (Jhonson et al., 2019).

3. Pathophysiology of Epilepsy

Epilepsy pathophysiology is a multi-step process and is caused by a momentary aberrant synchronization of neurons in the brain, which disrupts standard patterns of neuronal transmission and generates waxing and waning electrical discharges in the EEG (electrographic seizure)(Liu et al., 2017; Moshé et al., 2015). After extensive research, it has been discovered that there is an imbalance between glutamate (a major excitatory neurotransmitter) and gamma-aminobutyric acid (GABA) (the primary inhibitory) neurotransmitters (NTs), both of which play an essential role in epilepsy. (Aroniadou Anderjaska et al., 2008).

Voltage-gated channels, such as Na+, K+ and Ca2+ channels, are in a closed state at the resting membrane potential. When the cell membrane depolarises, the gate of the channel opens. During sustained depolarisation, the channel inactivates and remains in this refractory state for a limited period of time during repolarisation. Recovery from inactivation occurs, allowing further opening to happen. Ligand-gated channels can be activated by various neurotransmitters such as GABA and glutamate. Thus, ion channels also plays a role in epilepsy (Aroniadou Anderjaska et al., 2008).

Table 1: Current Management of Epilepsy with Antiepileptic Drugs.

DRUG	MECHANISM OF ACTION	EFFECTIVE AGAINST TYPE OF EPILEPSY	ADVERSE EFFECTS
Phenobarbital	Enhancement of GABA-meditated inhibition	First-line therapy for primary generalized tonic-clonic seizures	Sedation, fatigue, ataxia, blurry vision, Hyperactive (children) learning, depression
Phenytoin	Sodium channel blockers	Partial-onset and primary generalized tonic-clonicseizures: first-line treatment.	Gum hyperplasia, hirsutism, low thyroid, osteoporosis, Neuropathy
Topiramate	Na+ and Ca 2+ channel blockade Multiple (GABA potentiation, AMPA inhibition	Partially onset, primary generalised tonic-clonic, and myoclonic seizures are treated with TPM.	Mental retardation, speech, memory disturbance, paraesthesia, loss of weight and kidney stone
Lamotrigine	Sodium channel blocker, excitatory transmission attenuation	Effective against partial and generalized seizure	Headache, sleeplessness, stuttering, and tic
Gabapentin	Effects of blocking the Calcium channel ,2 subunit on GABA turnover	Effective against partial seizures	edema, behavioural changes in children and weight gain
Carbamazepine	Na + channel blocker	First line therapy for partial epilepsy	Behavioral changes, low sodium, weight gain/edema
Ethosuximide	Blockade of T-type of Ca 2+ channel	Absence seizures	Irritability, nervousness, confusion, psychosis, Behavioural changes
Zonisamide	Sodium and T-type Calcium channel blocker, carbonic anhydrase inhibition	Effective against partial and generalized seizures.	paraesthesia, weight loss, renal stones, apathy, Lost appetite, speech

Due to the treatment with antiepileptic drugs, the adverse effects alter the patient's life more particularly than seizures. The highly effective AEDs are typically associated with adverse effects (Table no. 1). Because synthetic drugs have hazards, alternate therapies should be employed to treat and manage epilepsy. Herbal remedies with fewer side effects than synthetic drugs can manage and treat epilepsy (Kr et al., 2014).

4. Herbals used for the Epilepsy Treatment

Nervine herbs are widely used to treat several nervous system disorders. These herbs are comparatively safer and have no known drug-herb interactions. These herbs can reduce seizure activity; intensity and mitigate some unfavourable cognitive and harmful side effects of anticonvulsant pharmaceuticals. The most prevalent agents in this category are as follows.

4.1. Brahmi

The botanical name for this plant is *Bacopa monnieri* (BM), which belongs to the Scrophulariaceae family. Bacoside-A, bacoside-B, glycosides, alkaloids, favonoids, saponins, and others are chemical components of Bacopa monnieri. CNS psychological illness is a common comorbidity of epilepsy, and BM has been shown to improve epilepsy-related impairments in cognition (Charoenphon et al., 2016). Brahmi vati (BV), an Ayurveda polyherbal formulation, demonstrated a significant hindlimb extension in a maximum electroshock model. After treating the animal with BM, significant downregulation of glutamate (Glu) receptor activity was observed, showing NMDA (N-methyl-D-aspartate receptor-1) expression reversal and Glu receptor binding alterations. In a similar study, the overexpression of the 5-HT2C (5-hydroxy-tryptamine2C) receptor was shown to be inhibited by BM in the Pilocarpine-induced epileptic rat's hippocampal area (Mishra et al., 2018). In addition, the forced swim test revealed that the depressive behaviour episode in the epileptic event in the rat brain was significantly reversed. Bacoside-A and BM are two different types of bacoside. In epileptic rats, BM improved performance in the Morris water maze test. A separate study showed that in pilocarpine-induced epileptic rats, there was a substantial reduction in GABAeric activity impairment in the brain (hippocampus, cerebral cortex, and cerebellum) areas (Shalini et al., 2021).

4.2. Jatamansi

Valeriana officinalis belongs to the Valerianaceae family. The volatile oil of sesquiterpenes (valerenic acid, valerian, valeranone, valepotriates) flavonoids, triterpenes, lignans and alkaloids are found in the roots and rhizomes of V. officinal (Nandhini et al.,2018). Valerian extract can cause drowsiness by raising GABA levels in the brain. GABA is an inhibitory neurotransmitter that, in high enough concentrations, can cause sedation. According to the findings of an *in vitro* investigation, GABA may be released from brain nerve terminals due to valerian extract and subsequently blocked from being reabsorbed by nerve impulses (Nandhini et al., 2018). Valrenic acid also inhibits the degradation of GABA by an enzyme, which is another method that valerian can boost GABA levels and help you get a good night's sleep. According to various studies, the level of GABA in the brain is increased by valerian root. GABA is a neurotransmitter that regulates nerve cells and relieves anxiety (Sahoo et al., 2018). In mice, the ethanolic extract of this plant shown to be effective against picrotoxin induced convulsions and it also antagonises the convulsions induced by PTZ and strychnine (Rezvani et al., 2010). Similarly, in adult zebrafish aqueous and ethanolic extracts of this plant increase the latency to PTZ-induced seizure in a concentration-dependent manner (Nandhini et al., 2018).

4.3. Red date

The botanical name of this plant is zizpus jujuba belonging to family rhamnaceae. It contains glycosides and flavonoids. It is used to make anticonvulsants. In rats, PTZ and MES-induced seizures can be reduced by a hydroalcoholic extract of zizyphus jujube fruits (Gao et al., 2013). In addition, the hydroalcoholic extract greatly enhances the anticonvulsant effects of Phenytoin and phenobarbitone in combination treatment without affecting their plasma concentrations (Abdollahi et al., 2013). The antiepileptic effect could be achieved by over excitation caused by Glu inhibition, NMDA synaptic release decrease, or imbalance of anti-oxidants. It can benefit rats with mental health issues and oxidative damage caused by seizures (Liu et al., 2017). Similarly, in rats, the hydroalcoholic extract ameliorates seizures and exhibits protection against generalised tonic-clonic seizures in PTZ model (Pahuja et al., 2011).

4.4. Linalool

It is derived from *Cinnamomum osmophloeum* belonging to the lauraceae family. The leaf of this plant contains camphor, as the main component along with cineol, eugenol, limonene, safrole, α-pinene, β-pinene and β-myrecene possesses potent anticonvulsant activity (Srikalyani et al., 2019). It has anticholinergic, neuroprotective and antioxidant properties as well. In mice cortical synaptosomes, it blocked K+ stimulated Glu release and worked as an NMDA receptor antagonist, resulting in a ninety percent decrease in Glu uptake (Zhu et al., 2014). This plant significantly ameliorated the frequency and severity of epileptic seizures in a dose-dependent manner in rats, in lithium pilocarpine induced seizures.

4.5. Devil helmet

It is an aconitum alkaloid derived from the *Aconitum napllus* belonging to family ranunculaceae. It contains beta-sitosterol, aconitine and songorine. It exerts molecular

actions in the rat hippocampus by potentiating GABA-A receptor inhibitory responses and inhibiting NMDA receptors (Hao et al., 2013). Blocking voltage-gated sodium ion channels also prevented hyperexcitability or depolarization of neurons. The active moiety in its structure, benzyl ester, is responsible for its antiepileptic properties. In an *in vitro* study, this phytochemical demonstrated dose-dependent action in rat brain slices at less than one molar concentration. It decreases the epileptic activity while being non-toxic (Kaur et al.,2021). Methanolic extract of this plant exhibited a significant reduction in the duration of hind limb extensor phase in MES model and delayed the latency of seizures induced by PTZ The anticonvulsant activity (Kalabharthi et al., 2021).

4.6. Berberine

It is aisoquinoline alkaloid found in *Berberis vulgaris* belonging to family berberidaceae. It contains isoquinoline alkaloids, tannins, phenolic compounds and sterols (Mohammadzadeh et al., 2017). Its anticonvulsant, antioxidant, antipsychotic, and depressive properties are well-known. It inhibited neuronal degeneration in the rat brain, improving neuron and hippocampus development. As a result, it has been suggested that it has antiepileptic properties similar to Phenytoin. Berberine also works as an NMDA receptor antagonist in the brain, preventing glutamate from binding to NMDA receptor (Zhu et al., 2013). It did not affect seizures caused by PTZ, indicating that GABAergic neurotransmission is not involved in berberine's antiepileptic mechanism. It's antidepressant properties and potential to ameliorate cognitive deficits suggest that it could be utilized to treat epilepsy with mental comorbidities. It hasn't caused any motor problems and could be an antiepileptic drug (Mojarad and Roghani, 2014).

4.7. Skullcap

It is a flavonoid from the *Scutellaria baicalensis* plant, belonging to the family lamiaceae. It contains flavones and other flavonoids. It has a substantial impact on the CNS. It works as an antiepileptic by enhancing the function of GABAergic neurons (Diniz et al., 2015). It relaxes the excitatory neuronal membrane by increasing the entry of chloride ions into the cell. It may serve as a partial agonist for GABA-A receptors in preclinical studies, enhancing its antiepileptic actions. It binds to the benzodiazepine (BZD) receptor with the most excellent affinity. *In vitro* and *in vivo* studies have demonstrated that it possesses anti-inflammatory, antioxidant, and neuroprotective properties. (Diniz et al., 2015). In adult Sprague Dawley rats this plant reduces the seizures induced by pilocarpine and also shown to be effective in inhibiting the continuous sodium current induced by NMDA receptors (Amtul, 2016)

4.8. Lavender

It is obtained from the *Lavandula officinalis* belonging to family Labiatae. This is another common herb used to treat epilepsy in Iranian traditional medicine. It contains linalool, linalyl acetate and camphor. In mice, it appears to have anticonvulsant characteristics in PTZ kindling and PTZ-induced seizures (Rahmati et al.,2013). It has been shown to protect cerebellar granular cells against Glu-induced neurotoxicity. Some investigations have shown that suppression of Glu release, augmentation of GABA receptors, Ca2+ channel blocking and antioxidant impact are probable reasons for its antiepileptic effect (Rahmati et al., 2013). The findings suggest that it has a great deal of promise for antiepileptic drug Research and Development.

4.9. Saikosaponin-A

It is a triterpene saponin derived from the *Bupleuri radix* plant belonging to family umbelliferae. This plant contains oleanane saponins, coumarin and several flavonoid derivatives. It's a significant bioactive molecule with various pharmacological properties, including anticonvulsant, anti-inflammatory, and neuroprotective properties. In hippocampal CA1 neurons of rats, it blocked Na+ channels and burst neuronal firing triggered by NMDA (Li et al., 2018). The role of mTOR hyperactivation in hippocampus neuron hyperexcitability has been explored. This drug prevented PTZ-induced seizures in PTZ-treated rats by lowering phosphorylated levels of mTOR and 70S6K proteins, indicating that it has antiepileptic potential (Li et al., 2018). This substance reduces glutamate synthase activity and elicit excitations that contribute to epileptogenesis were also suppressed.

4.10. Hemp

Plants that generate cannabidiol are *Cannabis indica* and *Cannabis sativa* and belonging to family cannabaceae. Cannabidiol (CBD), a phyto-cannabinoid, has been studied for its anticonvulsant properties in various seizure models. Although the exact mechanism of cannabidiol's antiepileptic action is unknown, several studies suggest that it works by reducing adenosine uptake by neuronal cells (Bialer et al., 2015; Mula et al., 2016). It can also activate cannabinoid (CA) receptors, but its affinity is lower than that of tetrahydrocannabinol which is likely why it has a lackluster psychotropic effect. It is also said to have a higher potency as a CA receptor antagonist (Bialer et al., 2015). It works as

partial agonist for the CB2 receptor while acting as a neutral antagonist for the CB1 receptor. It has been discovered that it affects several different target locations, including inhibitors of the equilibrative nucleoside transporter (ENT) system anda preventative measure of melastatin type-8 channels and orphan G protein-coupled receptors. Cannabidiol enhances the effects of 5HT-1A receptors and glycine receptors andintracellular Ca2+ion influx/efflux, indicating antiepileptic effects. In the pilocarpine-induced status epilepticus rat model, CBD attenuated maximum seizure severity following intravenous administration (Patra et al., 2019).

4.11. Kava

The word kava means bitter in the local language and belongs to the Piperaceae family. Kava's scientific name is *Piper methysticum*, which comes from the Latin word methysticum. Kavalactones and flavokavains are the active components in kava. Except for certain commonalities in the stated biological action, each class of molecule has its own set of characteristics. (Bian et al ., 2020). The anticonvulsant effect of kava root extracts is due to an increase in (GABA) type A receptors and ligands binding. Kavalactones such as Kavain, desmethoxyyangonin (DMY), and 7, 8 di-hydromethysticin are responsible for the anticonvulsant effect. These kavalactones can also be found in abundance in the Kava plant's stems and aerial portions, such as the leaves. PTZ (pentylenetetrazol-induced seizures) is an agonist of the receptor GABA-A, which cause seizure by altering the inhibitory effect of GABA, Therefore, in zebrafish model, aqueous extracts of KAVA showed anti-convulsant action in PTZ induced model (Jaiswal et al., 2020).

4.12. Sweet flag

The botanical name of this plant is *Acorus calamus* belonging to family Acoraceae. It contains alpha-asarone or beta-asarone's in roots and leaves. It has been shown to protect rats from stroke and chemically induced neurodegeneration (Chandra et al., 2017). It has a protective effect against acrylamide-induced neurotoxicity in particular. For hundreds of years, its roots and rhizomes have been utilized in Indian traditional medicine, and it is highly valued as a brain and nervous system rejuvenator. The elements of VACA rhizomes have many pharmacological characteristics, including sedatives, changing behavior, anti-epileptic, acetyl-cholinesterase (AChE) inhibitor and Memory boosting properties (Pattanaik et al., 2013).

4.13. Ashwagandha

The biological source of this plant is Withania somnifera belonging to family Solanaceae. The chemical constituent includes withanolides, steroids, saponins and glycosides (Singh et al., 2010). The root extract of this plant was administered before a lithium pilocarpine administration and it reduces the latency of forelimb clonus. It was also used in conjunction with typical antiepileptic medications (Soman et al., 2012). When it was coupled with these standard medicines, the effective doses of diazepam and clonazepam were dramatically reduced, resulting in full protection with no mortality. In adult rats, this plant showed anti-convulsant action in PTZ induced seizures. This plant is used to treat temporal lobe epilepsy in rodents (Anju et al., 2018).

Table 2: Medicinal plants used in epilepsy.

Sr. No.	Common name	Biological source	Chemical constituents
1	Brahmi	Bacopa monnieri	Bacoside-A, bacoside-B, Glycosides, Alkaloids, Flavonoids, Saponins
2	Jatamansi	Valeriana officinalis	Valerenic acid, Valerian, Valeranone, Valepotriates, Flavonoids, Triterpenes, Lignans and alkaloids
3	Red date	zizpus jujuba	Glycosides and Flavonoids
4	Linalool	Cinnamomum osmophloeum	Cineol, Eugenol, Limonene, Safrole, α-pinene, β-pinene and β-myrecene
5	Devil helmet	Aconitum napllus	Beta-sitosterol, Aconitine and Songorine
6	Berberine	Berberis vulgaris	Isoquinoline alkaloids, Tannins, Phenolic compounds and Sterols
7	Skull cap	Scutellaria baicalensis	Flavones and other Flavonoids
8	Lavender	Lavandula officinalis	Linalool, Linalyl acetate and Camphor

9	Saikosaponin-A	Bupleuri radix	Oleanane saponins, Coumarin and several flavonoid derivatives
10	Hemp	Cannabis indica Cannabis sativa	Carbohydrates, Cannabinoids, Proteins and fibres
11	KAVA	Piper methysticum	Kavalactones and flavokavains
12	Sweet flag	Acorus calamus	alpha-asarone or beta-asarone's
13	Ashwagandha	Withania somnifera	Withanolides, Steroids, Saponins and Glycosides

5. Conclusion and Future Aspects

Epilepsy is a brain illness caused byan imbalance between the glutamate and GABAneurotransmitter of the brain, and it affects nearly 70 million of the world population. Currentlyused synthetic AED medication is being for cure seizures. These drugs directly act on GABA and NMDA receptors and help treat epilepsy. But still is found that these medications has not shown efficacy in nearly 30% of the affected population and show many adverse effects that are fatal for life. In the ongoing research in the field of herbal medicines also shows the exact mechanism as synthetic drugs by acting on GABA and NMDA receptors, herbals show good efficacy without showing any fatal adverse effects.

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