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A SYSTEMATIC REVIEW OF THE PROTECTIVE EFFECT OF MEDICINAL PLANTS IN THE TREATMENT OF EPILEPSY

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ABSTRACT

Throughout history, plants have played a significant role in providing relief and healing through their therapeutic properties. These natural remedies contain active compounds that directly impact various organs in our bodies, including the complex organ that is the brain. While only a few drugs have been approved for conditions like epilepsy, ancient systems of medicine like Ayurveda have long categorized plants that can affect the brain. Epilepsy, a neuropsychological disorder, is characterized by the overactivity of neurotransmitters. It is distinct from seizures, which are sudden, abnormal bursts of activity in the central nervous system. Modern medicine offers numerous drugs for epilepsy treatment, but many come with chronic side effects. As a result, the use of herbal remedies as adjunct therapies is becoming increasingly popular due to their milder side effects. These plant-based treatments often target the same mechanisms as synthetic drugs. Traditional medicine has long relied on various plant-based remedies for epilepsy, and ongoing research is now scientifically validating their anticonvulsant properties. This article summarizes recent research on medicinal plants with reported antiepileptic/anticonvulsant effects. It provides pharmacological and molecular mechanism of action information for the crude extracts and related active constituents evaluated in preclinical research for the treatment of epilepsy and convulsions, and offers a reference for the development of future related studies in this area.

KEYWORDS: Epilepsy, Antiepileptic drugs, Seizures, Medicinal plants.

INTRODUCTION

Epilepsy, a prevalent chronic neurological disorder, is marked by recurring seizures due to atypical neuronal activity. It impacts approximately 50 million individuals globally and is marked by the repeated occurrence of seizures, which are the outward signs of abnormal brain activity. Seizures can manifest in a variety of ways, reflecting the location, extent, and propagation of the abnormal neuronal activity (Chipiti et al., 2021). Seizures are fundamentally divided into two major groups: partial and generalized. Partial (focal, local) seizures are those in which clinical or electrographic evidence exists to suggest that the attacks have a localized onset in the brain, usually in a portion of one hemisphere, while generalized seizures are those in which evidence for a localized onset is lacking. Partial seizures are further subdivided into simple partial, complex partial and partial seizures evolving to secondarily generalized seizures, while generalized seizures are categorized into absence (nonconvulsive), myoclonic, clonic, tonic, tonic-clonic and atonic seizures (Wirell et al., 2022). As such, epilepsy is now understood as a spectrum of distinct clinical manifestations rather than a singular disease. Different types of seizures can be distinguished based on their clinical features. While there are numerous antiepileptic drugs available to manage epilepsy and reduce the frequency and intensity of seizures, these medications may not work equally well for all patients. Ideal treatments would effectively control all seizures without adverse side effects. However, current medications often fall short of this goal, proving ineffective for some individuals and causing undesirable side effects in many cases (Vyawahare et al., 2007). It is essential to develop effective drug therapies that can address both epilepsy ultimately enhancing the quality of life for individuals living with epilepsy (Suvarna and Gandhi, 2016).

Modern Antiepileptic Drugs (AEDs) and Their Adverse Effects: Classification Based on Mechanism of Action

Sodium Channel Blockers (Na^+ Channel Modulators) : These AEDs work by inhibiting the rapid firing of neurons by blocking sodium channels during

depolarization. This helps to stabilize the neuronal membrane and prevent the spread of seizure activity.

Calcium Channel Blockers (Ca^{2+} Channel Modulators): These AEDs work by blocking T-type calcium channels, particularly in thalamic neurons, which are involved in certain types of seizures, such as absence seizures.

GABAergic Drugs (Gamma-Aminobutyric Acid Modulation): These AEDs enhance the inhibitory effects of GABA, the major inhibitory neurotransmitter in the brain. By increasing GABAergic activity, these drugs help to reduce neuronal excitability and prevent seizures.

Glutamate Antagonists: Glutamate is the primary excitatory neurotransmitter in the brain. Drugs that block glutamate receptors, particularly the NMDA (N-methyl-D-aspartate) receptor, help to reduce excitatory neurotransmission and prevent seizures.

Adverse effects: Sedation, dizziness, vertigo, diplopia, ataxia, vomiting, diarrhea and anorexia. Acute intoxication causes coma, convulsion and cardiovascular collapse. Hypersensitivity reactions are rashes, photosensitivity, hepatitis, lupus like syndrome. Some degree of leucopoenia, due to hypersensitivity is more common. They are also teratogenic in nature. Due to the intense side effect of modern drug treatment, the herbal treatment is gaining more popularity. They are safe in use as compared to conventional drug treatment.

Several studies have been reported on the efficacy of plant extracts and phytochemicals against various diseases related to the central nervous. Curcumin, generally used as a spice in food, is reported to have a promising ant neurodegenerative effect in animal models and also in humans, especially against dementia. In addition, spicatoside, resveratrol, broccoli, and many more have been studied for their effect against various neurological and neuroprotective efficacy. Moreover, medicinal plants (phytochemicals and metabolites) have been extensively used for the treatment of various neurological diseases, especially epilepsy in most of the low- or middle-income countries. Plants possess diverse medicinal properties attributed to the presence of various phytochemicals. In traditional medicine, plants are utilized to treat a wide range of health conditions, including epilepsy. The active components present in plants exert direct pharmacological effects on the body, affecting different organs through mechanisms similar to synthetic drugs (Loshali et al., 2021). Essential oils extracted from plants have shown significant efficacy in reducing seizures by inducing a calming and relaxing effect (de Almeida et al., 2011).

MATERIALS AND METHODS

Articles related to ethnopharmacological and antiepileptic studies on plants were collected from PubMed, Web of Science and Scopus, etc. using keywords related to epilepsy, medicinal plants, and natural products, etc.

Anticonvulsant Medicinal plants

Abutilon indicum

Abutilon indicum, also known as "Thuthi," is a plant belonging to the Malvaceae family and is commonly found in the hotter regions of India. Studies have shown that this herb demonstrates a significant protective effect at doses of 100 mg/kg and 400 mg/kg against known epileptic agents. This protective effect is attributed to the presence of certain fatty acids and flavonoids in the plant, such as linoleic acid and flavonoid compounds. The results of the study indicate that Abutilon indicum exhibits strong anticonvulsant properties, making it a potentially beneficial treatment for various types of epilepsy, including Grand mal and Petit mal epilepsy (Suvarna and Gandhi et al., 2016).

Brahmi ghrita

Brahmi ghrita is a polyherbal formulation belonging to the Scrophulariaceae family. It contains a mixture of Bocopa monnieri (4%), Evolvulus alsinoides (4%), Acorus calamus (4%), and Saussurea Lappa (4%), combined with cow's ghee (84%) and suspended in 1% acacia. This formulation is administered to Swiss albino mice weighing 25g. It has been shown to reduce alertness and spontaneous locomotory activity in mice. Additionally, it counteracts the behavioural effects of d-amphetamine and provides protection against electroshock and pentylene tetrazole-induced convulsions (Achaliya et al., 2005).

Catharanthus roseus

Catharanthus roseus, commonly known as vinca, belongs to the Apocynaceae family. This evergreen sub herb or herbaceous plant can grow up to 1 meter tall. It produces over 100 different terpenoid indole alkaloids and is a commercial source of anti-cancer terpenoid indole alkaloids (Shinde et al., 2017). Traditionally, Catharanthus roseus has been used as a diuretic, astringent, and for treating conditions such as cough, wasp stings, nosebleeds, sore throats, mouth ulcers, and bleeding gums (Nishanth et al., 2018). The roots of Catharanthus roseus, particularly the SW petroleum ether extract, contain these active constituents. At a dose of 400 mg/kg, this extract has shown significant anticonvulsant activity, leading to a notable reduction in the duration of the extensor, clonus, and stupor phases compared to the control group.

Oscimum sanctum

Ethanolic extract of Oscimum sanctum (OS) leaves is used to treat haloperidol-induced catalepsy (1.0 mg/kg, intraperitoneal). Belonging to the Lamiaceae family, this extract was tested on albino mice, which were divided into several groups, each containing six animals. The effects of the test drug OS (at doses of 1.75, 4.25, and 8.5 mg/kg) and the standard drugs scopolamine (1.0 mg/kg)

and ondansetron (0.5 and 1.0 mg/kg) were assessed after single and repeated dose administration for seven days, administered 30 minutes prior to haloperidol. The results suggest that the ethanolic extract of OS has a protective effect against haloperidol-induced catalepsy (Pemminati et al., 2007).

Leuca scephalotes

Leucas cephalotes, belonging to the Lamiaceae family, is known as "Dronapushpi" in Sanskrit and "Gumma" in the local language. The decoction of its dried aerial parts is used orally to treat diarrhea, reduce fever, and act as an appetizer. It is also used to treat jaundice, colds, and coughs (Das et al., 2012). Leucas cephalotes may exhibit a mechanism similar to diazepam, providing 100% protection against seizures. Isoniazid (INH) is commonly used for the treatment and chemoprophylaxis of tuberculosis but can cause serious central nervous system (CNS) side effects, including seizures and comas, due to inhibition of GABA synthesis. Diazepam-treated groups showed up to 100% protection of animals, whereas the PLC was ineffective in providing protection. However, the ELC was found to be more effective than the PLC, suggesting that the extract may work either by enhancing L-glutamate or inhibiting GABA degradation by GABA transaminase (Chimbalkar et al., 2016).

Saussurea lappa

The roots of Saussurea Lappa, belonging to the Asteraceae family, are traditionally used in Ayurvedic medicine to treat epilepsy. The anticonvulsant activity of Saussurea Lappa was evaluated using petroleum ether extract (SLP), alcoholic extract (SLA), and water extract (SLW) against pentylenetetrazole and picrotoxin-induced convulsions, as well as the maximal electroshock (MES) test in mice. Pharmacological screening revealed that SLP (100 mg/kg i.p.) and SLA (300 mg/kg i.p.) significantly increased the latency to colonic convulsions and reduced mortality in mice treated with pentylenetetrazole and picrotoxin. SLW (300 mg/kg i.p.) also significantly increased the latency to clonic convulsions, reduced the number of convulsion episodes, and decreased mortality. Additionally, SLP (100 and 300 mg/kg i.p.), SLA (100 and 1000 mg/kg i.p.), and SLW (100 and 1000 mg/kg i.p.) reduced mortality in the electroshock experiment (Shirishkumar et al., 2009).

Taxus wallichiana

Taxus wallichiana belonging to the family Taxaceae, has an extract that controls pentylenetetrazole induced convulsions in mice. At doses of 100 and 200 mg/kg i.e., the extract significantly inhibited myoclonus and clonus, while the inhibition of tonus and hind limb tonic extension (HLTE) was highly significant ($P < 0.01$). This study reports the anticonvulsant activity of Taxus wallichiana for the first time within the entire genus. These pharmacological activities provide scientific support for the traditional use of the plant in treating epilepsy (Nisar Muhammad et al., 2008).

Viola tricolor

Viola tricolor L. (V. tricolur), commonly known as wild pansy, is a member of the family Violaceae. In the Indian traditional medicine system, it is used to treat various skin disorders, bronchitis, and has anti-inflammatory, cough expectorant, and diuretic properties. These medicinal properties are largely attributed to the presence of saponins, flavonoids, adhesives, salicylic derivatives, and carotenoids (Rahimi et al., 2009). A study suggests that V. tricolor and its ethyl acetate and n-butanol fractions exhibit anticonvulsant activity. This is confirmed by the prolongation of latency to the first generalized tonic-clonic seizures (GTCs) induced by pentylenetetrazole (PTZ) and a reduction in the incidence of hind limb tonic extension (HLTE) induced by maximal electroshock (MES) (Toiu et al., 2009).

Mimosa pudica

The decoction of Mimosa pudica leaves given intraperitoneally at dose of 1000–4000 mg/kg protected mice against pentylenetetrazol and strychnine-induced seizures. M. pudica had no effect against picrotoxin-induced seizures. It also antagonized N-methyl- -aspartate- induced turning behaviour. These properties justified its use in African traditional medicine (Ngo Bum et al., 2004).

Sphaeranthus indicus

Hydroalcoholic extract of Sphaeranthus indicus showed anticonvulsant activity against pentelyenetetrazole and maximum electroshock, 500 mg/kg of Sphaeranthus indicus was found to significantly decrease the duration of the hind limb tonic extensor phase in MES-induced seizures whereas the lower dose (100 and 200 mg/kg) has not give any protection (100, 200 and 500 mg/kg). In PTZ induced seizure dose dependents reduction in the duration of the first clonic convulsion in mice was seen (Galani et al., 2010).

Centella asiatica

Aqueous extract of Centella asiatica (Mackinlayaceae) are shown in Figure 11 (100 and 300 mg/kg) was tested for its anticonvulsant activity against pentylenetetrazole (30 mg/kg i.p). The extract at the dosage of 300 mg/kg orally decreased the PTZ kindled seizures and improvement in the learning deficit and low dose (100 mg/kg) failed to improve the seizure, it improved only the learning deficit (Gupta et al., 2003).

Epilepsy, oxidative stress and Antioxidants

Cellular damage and disruption of cellular functions can result from oxidative stress, leading to cell death by oxidizing biomolecules like lipids, proteins, and nucleotides. The occurrence of seizures may be linked to an imbalance in antioxidants and oxidants, known as oxidative stress, where there is an excess of reactive oxygen species (ROS) and reactive nitrogen species Sudha et al., 2001). The levels of ROS are carefully controlled to carry out important functions such as autophagy, cell division, chemical signalling, and

signalling for mitogen-activated protein kinases and apoptosis (Gluck et al., 2000). Due to their high reactivity, ROS are tightly regulated. Seizures during epileptogenesis are often followed by mitochondrial dysfunction induced by ROS (Frantseva et al., 2000).

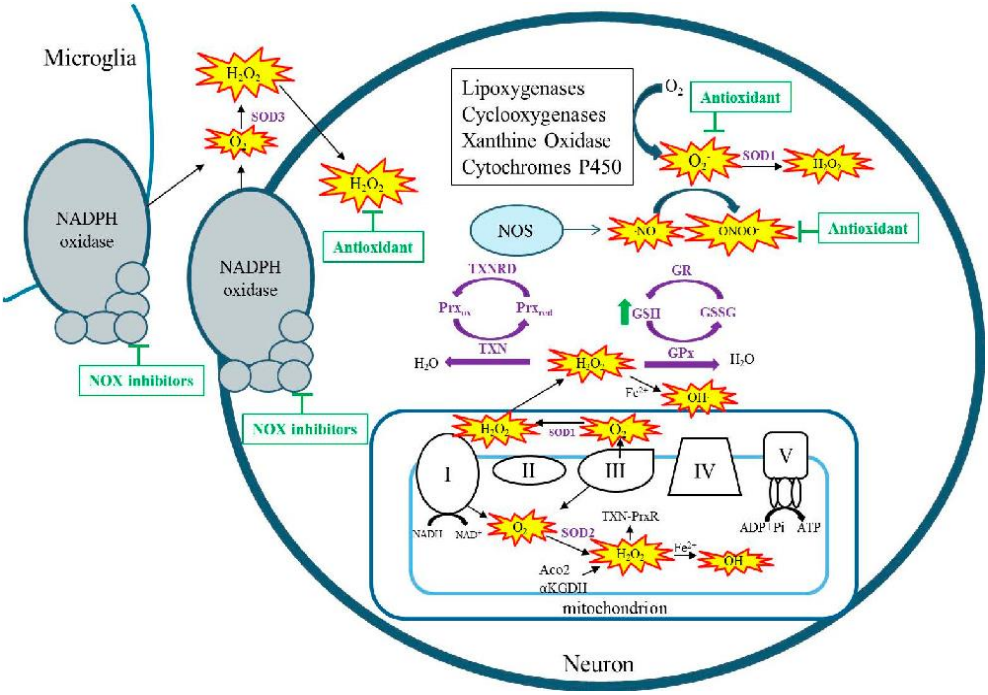

Figure 1: Cellular sources of reactive species (RS). RSs are denoted by yellow starbursts. Antioxidant systems and their detoxification of RS are denoted in purple and purple arrows, respectively. Therapeutic strategies for detoxification of seizure-induced RSS are denoted by green arrows, indicating elevating GSH or t-bars indicating inhibition by antioxidants or NOX inhibitors. NOS: nitric oxide synthase; GSH: reduced glutathione; GR: Glutathione reductase; GSSG: oxidized glutathione; GPx: Glutathione peroxidase; SOD: superoxide dismutase; TXN: thioredoxin; TXNRD: thioredoxin reductase; Prxox: peroxiredoxin oxidized; Prxred: peroxiredoxin reduced; Aco2: aconitase; A-KGDH: alpha-ketoglutarate dehydrogenase.

During an epileptic seizure, there is a notable increase in calcium influx through voltage-gated and NMDA-dependent ion channels. This surge in intracellular calcium levels can lead to the production of reactive oxygen species (ROS) (Coyle et al., 1993), triggering biochemical cascades. To counteract ROS, the body activates enzymatic antioxidant defense systems such as superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase, and peroxiredoxins. Additionally, non-enzymatic antioxidants like vitamin C, vitamin E, and reduced glutathione (GSH) play a role in combating oxidative stress. The exploration of antioxidant therapies for managing epilepsy has attracted significant attention in the field of treatment.

Several studies have demonstrated the antioxidant properties of Artemisia extracts in preventing oxidative stress and providing neuroprotection through the regulation of endogenous antioxidants. These extracts have been found to enhance the antioxidant capacity of both serum and brain tissue. Moreover, the use of Artemisia extracts has been associated with a decrease in spinning and jumping behaviour in epileptic mice, as well as a reduction in tonic seizures. Notably, the anticonvulsant effects of A. persica extracts can be amplified by diazepam, while flumazenil has the opposite effect. Analysis of brain tissue has revealed decreased expression of IL-1β and TNF-α in the brains of PTZ-treated mice following treatment with A. persica (Daneshkhah and Setorki., 2019).

Silybum marianum is a natural remedy known for its anticonvulsive properties, acting as an antioxidant and antiseizure agent. It has been shown to decrease both the frequency and duration of convulsions in PTZ experimental mice and lower PTZ-induced lethality.[25] These effects are partially attributed to the reduction of oxidative stress in the brain, evidenced by increased activity of superoxide dismutase and catalase, and a decrease in lipid peroxidation levels. Additionally, the antioxidant properties of Gastrodia elata, a traditional Chinese medicinal herb containing gastrodin as its active ingredient, have shown beneficial effects on various neurological disorders such as epilepsy, Alzheimer's disease, and Parkinson's disease in preclinical studies (Waqar et al., 2016).

Research conducted by Kong et al. indicates that treatment with antioxidant substances like SOD mimetics, melatonin, and vitamin C can help partially prevent induced seizures. In their study on epileptogenesis, the researchers found that RNA

oxidation plays a significant role in the process. By using pilocarpine to induce status epilepticus (SE) in rats, they observed a notable increase in RNA oxidation in vulnerable neurons, leading to neuronal death (Liu et al., 2018). However, administering antioxidants like coenzyme Q10 on a daily basis effectively reduced RNA oxidation levels and shielded the rats from SE-induced neuronal loss. These findings suggest that RNA oxidation may be a crucial factor contributing to neurodegeneration in seizures caused by neuronal activity and epileptogenesis.

In their study, Sudha et al. examined various parameters related to oxidative stress, such as lipid peroxidation, superoxide dismutase (SOD), glutathione peroxidase (GP), glutathione reductase (GR), and catalase, as well as levels of antioxidant substances like vitamin C, vitamin E, vitamin A, and ceruloplasmin activities in both epileptic patients and normal controls. Patients who had been undergoing treatment with phenobarbital and had not experienced convulsions for a year were selected for further evaluation. The study found that levels of lipid peroxidation in epileptic patients were significantly higher compared to the control group (Kong and Lin., 2010). Additionally, plasma concentrations of ceruloplasmin were notably elevated in the epileptic cases. On the other hand, levels of plasma vitamin C and A were significantly lower in epileptic individuals when compared to the controls. Upon follow-up, patients showed a significant increase in GR levels compared to their pre-treatment condition. Moreover, plasma concentrations of vitamin A, E, and C in the follow-up patients remained within normal ranges. These findings suggest that the antioxidant status in the blood of epileptic patients, initially lower than that of controls, improved after treatment with antiepileptic drugs (AED), indicating a potential involvement of free radicals in the development of epilepsy.

CONCLUSION

The present review revealed the anticonvulsant activity of Indian medicinal plants those have been tested in vivo. Crude extracts was used for in vivo studies, the bioactive components from all those plants have to be isolated and tested in vivo/in vitro, molecular interactions with various epileptic targets have to be studied which provides vital results. Traditionally, herbal medicines have been used for decades as a remedy for many diseases. The epileptic activity of plants plays an important vital in herbal medicines exhibited able anticonvulsant properties and low toxicity in the experimental model at the doses used. However, further studies still needed to be carried on an exhibit of the extract to people, and it's used in folk medications for seizure control should be including by regular assessment of the level of consciousness and blood pressure. This reviews an overview of the antiepileptic activity in traditional medicinal plants as able use for the development of new medicines used in the protection against epileptic activity. However, we can safely state that herbal medicines have enormously able to provide some remarkable drugs.

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