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NATURAL PERSPECTIVE ON ANTI-EPILEPTIC ACTIVITY OF HERBAL PLANTS

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ABSTRACT:

Traditional herbal treatments are becoming increasingly popular in international discourse, particularly in relation to the treatment of epilepsy. Over 50 million people worldwide are said to be afflicted by this fatal illness. Neurotransmitter molecule release and an excess of electric discharge in the brain are thought to be the causes of this neurological condition. Despite their benefits, antiepileptic medications are costly and hard to come by. Above all, one has to endure unsatisfactory consequences and worthless compromises. Numerous studies are included in this study that show how beneficial over thirty herbal remedial plants and their extracts are for treating epilepsy and preventing its repercussions. These plants go by the names *Adansoniadigitata, Abutilonindicum, Vitex negundo, Allium cepa, Annona senegalenesis, Acormuscalamus, Aegle marmelos, Biophytum sensitivum, Butea monosperm, Datura metal, and Acormuscalamus. Citrus sinesis, Lobelia nicotinaefolia, Viola tricolour, Leucascephalotes, Phyllanthus marus, Pletranthusbarbatus, Ocimum sanctum, Nepetabractaeta, Nardostachys jatamansi, Mahua longifolia, Milicia excels, Citrus colocynthis, Acalypha fruitcosa, Cocos nucifera, Lobelia nicotinaefolia, Citrus sinesis, Carissa edulis, Commiphora weightti, Clerodendrum infortunatum, Desmodium triflorum, and Catharanthus roseus*. Certain medicinal herbs have been demonstrated to decrease methylmaldehyde (MDA), lipid peroxidation, and enhanced glutathione (GSH). These are some of the mechanisms of action linked to epilepsy brought on by lithium-pilocarpine, pentylenetetrazole (PTZ), maximal electroshocks (MES), isoniazid (INH), strychnine, and other medications. Animal tests on these possible herbal medicines show encouraging outcomes. Clinical trials and rigorous research methods would undoubtedly result in a considerable advancement in the use of traditional herbal medicines to treat epilepsy.

1. INTRODUCTION

According to WHO (1), 2.4 million cases of epilepsy are reported annually, affecting over 50 million people worldwide. Studies on epilepsy have shown that 70% of people can live seizure-free lives with the right diagnosis and care (2). An estimated 6.38 cases of active epilepsy are reported for every 1000 persons, with an annual prevalence rate of 61.44 cases per 100,000 persons, according to a recent study (3). Social, physical, and overall quality of life are all greatly impacted by epilepsy (4). Abnormal and periodic discharge of neurons in the brain is the hallmark of epilepsy, a common and frequently fatal disorder. Frequent and unpredictable seizures are the hallmark of epilepsy, a persistent neurological condition.

Muscle spasms, contractions, loss of consciousness, and seizures can all result from the brain's incapacity to receive messages 5. At the synapse, an imbalance between excitatory and inhibitory drive may cause seizures. Try prolonging the duration of Na+ channel inactivation, enhancing GABA synaptic transmission, and blocking Ca+ channel opening to stop seizures. Research has shown that GABA and GABA receptors play a major part in the antiepileptic effects of herbal remedies (6).

1.1 GABAergic mechanism

Approximately 40% of synapses in the brain release GABA, the principal inhibitory neurotransmitter in the central nervous system. This chemical is produced from glutamate by the enzyme glutamic acid decarboxylase (7). Hyperpolarization results from GABA release activating GABAA, GABAB, and GABAC receptors. Ligand-gated ion channels are what the GABAA and GABAC receptors are. GABA binding opens the pore of GABA and GABA receptors to the passage of bicarbonate and chloride (8). There are five different protein subunits in the mammalian GABAA receptor: two α, two β, and a fifth that could be either γ or δ. Short-lived, continuous desensitising currents are mediated by GABAA receptors at synapses using α, β, and γ subunits, while long-lasting, progressive desensitisation is mediated by GABAA receptors at extra synaptic sites using α, β, and δ subunits (9). The G-protein coupled receptor (GPCR) GABAB hyperpolarizes potassium channels and reduces calcium entry, resulting in both excitatory and inhibitory effects (7). The pituitary, gastrointestinal tract, spinal cord, and retina all contain the rho, α, and β subunits of the GABAC receptor. Bicuculline has little effect on this receptor. Its distribution and abundance in the central nervous system are less than that of GABAA receptors(10).It is possible to treat epilepsy using antiepileptic medications, but their side effects may make them less desirable (11). Since they have few adverse effects and can effectively treat seizures over the long term, herbal therapies and complementary medicine are becoming more and more popular.

1.2 Global Scenario

An estimated 5 million individuals global are identified with epilepsy each year. It is estimated that 49 out of every 1,00,000 people in high-income countries suffer from epilepsy each year. In low- and middle-income nations, this ratio can increase to 139 per 100,000 people. The greater risk of prevalent diseases like malaria or neurocysticercosis; the greater frequency of traffic accidents; birth-related injuries; and disparities in access to care, medical facilities, and preventative health initiatives are most likely the causes of this. Approximately 80% of epileptics reside in low- and middle-income nations.

Table 1 Epilepsy Worldwide Epidemiology and India's and adjacent nations' relative prevalence

Epilepsy	**Prevalence**	**References**
Worldwide	0.5-1%	Hussain et al.,2017
Asia	0.49%	Khan et al., 2019
Africa	1.13%	Khan et al., 2019
Australia	0.44%	Bellon et al., 2015
Europe	0.82%	Khan et al., 2019
North America	0.8%	Theodore et al., 2006

1.3 Traditional Therapy

As innovative, safe treatment options, a few medicinal plants have shown promise [15–16]. All around the world, mental illnesses such schizophrenia, alcoholism, Parkinson's, Alzheimer's, and epilepsy are considered serious problems (Chang et al., 2013). This includes depression. Table 1 shows the incidence of epilepsy in India and the surrounding countries as well as the global epidemiology of the condition. According to Penfield and Erickson (1941), an epileptic seizure is "a state produced by an abnormal excessive neuronal discharge within the central nervous system." The brain's neurons fire more often and synchronously during seizures, which results in paroxysmal alterations in neuronal function. An epileptic

seizure is identified when it is differentiated from a non-epileptic event, such as a psychogenic seizure, and is brought on by aberrant neural activity.

The most popular kind of treatment for epilepsy is the use of antiepileptic drugs (AEDs).By preventing discharge and inducing hypnosis, they are used to manage convulsions. Synthetic AEDs such as phenytoin, phenobarbital, carbamazepine, primidone, and valproate are readily available in practice. Plants have a vast array of medicinal properties due to the presence of various phytochemicals. Plants used in folk medicine are used to treat a wide range of illnesses, including epilepsy. Plant active ingredients work through the same mode of action as synthetic drugs to directly affect the pharmacological profile of the human body, including several organs [5]. Many essential oils made from plants have a significant effect on seizures because they are soothing and relaxing [6].

1.4 Role of herbs in the treatment of epilepsy

Due to the unfavorable side effects, exorbitant cost, and limited effectiveness of synthetic medications, medicinal plants are being investigated for the treatment of epilepsy. Because they are less expensive, most underdeveloped nations rely on plants.14. Table 2 lists the medicinal plants that have been studied for their potential to be anti-epileptic.

TABLE 2: list of natural medications used in epilepsy

S.No.	Biological Name/Family	Common Name	Part	Extract/Dose
1.	*Adansonia digitata L.* [Malvaceae]	Baobab	Bark, Stem	Methanolic 1500, 750 & 375 mg/kg
2.	*Abutilion indicum* [Malvaceae]	Thuthi	Leaf	Aqueous and Ethanolic 100 & 400 mg/kg
3.	*Allium cepa L.* [Alliaceae]	Onion	Bulb	Methanolic 200 & 400 mg/kg
4.	*Annona senegalenesis* [Annonaceae]	Wild custard apple	Root	Aqueous 50,100,200,400 & 800 mg/kg
5.	*Acorus calamus* [Araceae]	Vacha	Rhizome	Ethanolic250 & 500 mg/kg
6.	*Aegle marmelos* [Rutaceae]	Bael	Leaves	Ethanolic100 & 200 mg/kg
7.	*Biophytum sensitivum* [Oxalidaceae]	Little tree plant	Leaf	Ethanolic 50,100 & 200mg/kg
8.	*Butea monosperma* [Fabaceae]	Flame of Forest	Stem	Methanolic 100, 200 & 300 mg/kg
9.	*Canna indica L.* [Cannaceae]	Edible canna	Aerial	Methanolic 100, 200& 400 mg/kg
10.	*Datura metal* [Solanaceae]	Devil's trumpet	Leaf	Ethanolic 200 & 400 mg/kg
11.	*Cocos nucifera L.* [Arecaeae]	Palm tree	Root	Aqueous 50& 100 mg/kg
12.	*Citrullus colocynthis* [Curcurbitaceae]	Bitter apple	Fruit	Hydroalcholic 10,25,50&100mg/kg
13.	*Acalypha fruticosa* [Euphorbiaceae]	Chinniche di	Aerial	Chloroform 30,100&300mg/kg
14.	*Carissa edulis*	Natal plum	Root	Aqueous 150, 300 &

	[Apocynaceae]			600 mg/kg
15.	*Commiphora weightii* [Burseraceae]	Indian bdellium	Resin	Oleogum resin 200 & 400 mg/kg
16.	*Clerodendrum infortunatum L.* [Verbenaceae]	Glory bower	Leaves	Ethanolic 400, 600 & 800 mg/kg
17.	*Desmodium triflorum* [Fabaceae]	Creeking tick trefoil	Leaves	Ethanolic 400 & 800 mg/kg
18.	*Citrus senesis* [Rutaceae]	Sweet orange	Leaf	Hydroethanolic 50 & 100 mg/kg
19.	*Lobelia nicotinaefolia* [Campanulaceae]	Tabacco	Leaf	Hydroalcholic 5, 10, 20 & 30 mg/kg
20.	*Viola tricolor* [Violaceae]	Johnny jump up	Leaves	Hydroalcholic 100, 200 & 400 mg/kg
21.	*Leuca scephalotes* [Labitatae]	Dronpushpi	Whole plant	Ethanolic & Petroleum 20, 40 & 60 mg/kg
22.	*Phyllanthus amarus* [Euphorbiaceae]	Herbaceous plant	Leaves , Stem	Aqueous & Ethanolic 70mg/kg
23.	*Plectranthus barbatus* [Lamiaceae]	Indian coleus	Leaves	Hydroalcholic 1,10,30&100mg/kg
24.	*Ocimum sanctum* [Lamiaceae]	Tulsi	Leaves	Ethanolic 1.75, 4.25 & 8.50 mg/kg
25.	*Nepeta bractaeta* [Lamiaceae]	Nepeta	Flower	Methanolic & Aqueous 190 & cut 560mg/kg
26.	*Nardostachys jatamansi* [Caprifoliaceae]	Jatamansi	Root	Ethanolic 200&400mg/kg
27.	*Mahua longifolia* [Sapotaceae]	Mahuwa	Wood	Aqeous 100,200&400mg/kg
28.	*Milicia excels* [Moraceae]	Iroko tree	Leaf	Ethanolic 250,500&1000mg/kg
29.	*Catharanthus roseus* [Apocynaceae]	Vinca	Leaf	Petroleum ether 100, 200 & 400 mg/kg
30.	*Vitex negundo* [Verbenaceae]	Horseshoe vitex	Leaf	Methanolic 200 & 400 mg/kg

1.5 Antiepileptic Herbal Drugs :

1. ***Abutilon indicum*:** Malvaceae is the family from which *Abutilon indicum* belongs. It's commonly known as "Thuthi". All of India's hotter regions are home to it. There is evidence from the herb that AIE at doses of 100 mg/kg and 400 mg/kg has a strong protective effect against recognised epileptic drugs. certain data indicates that this fatty acid acts as an anticonvulsant, as do certain flavonoids. The extracts show that *Abutilon indicum* has anti-seizure properties due to the presence of linoleic acid and/or flavonoid components. It appears that AIE may help treat both forms of epileptic illnesses, such as Grand mal and Petit mal epilepsy (19), as both doses demonstrated a very strong and impressive antiepileptic action.

2. ***Allium cepa L:*** A member of the *Alliaceae family* is Allium cepa Linn. Most people call it an onion.It is a herb that grows every two years, but it can also be a perennial. It has multiple blossoms, a meaty, underground bulb, and linear, hollow leaves. The natural plant known as *Allium cepa L*, or red onion, is frequently used as a spice and condiment in cuisine. Glutathione, selenium, and vitamin C are among the antioxidants included in *Allium cepa Linn*. Flavonoids including isorhamnetin (16) and quercetin are also present. The metabolomes of garlic and onions were analysed for molecules containing sulphur, genotype authentication, and antibacterial properties (16,21,22,23). Allium cepa bulb methanol extracts have anxiolytic and anticonvulsant properties that may be partially mediated by GABA transmission activation. To separate the active components and identify the precise mechanism of action, more investigation is required. The aetiology of a number of neuropsychiatric disorders appears to be influenced by GABA. It is well recognised that many older pharmaceuticals that are used to treat mental illnesses work, at least somewhat, by increasing GABA activity. However, some more recent medications may only act by activating GABAergic receptors. Treatment with 200 and 400 mg/kg of MEAC caused a considerable rise in wholebrain GABA levels relative to the control.

3. ***Annona senegalenesis:*** A member of the Annonaceae family is *Annona senegalenesis*. A wild custard apple is another name for it. It is also used in conjunction with other herbs to treat snake bites, toothache, dysentery, diarrhoea, and digestive diseases. Worm infestation, sleeping sickness, and sexual illnesses are among the conditions it cures. The root extract of *A. senegalenesis* was aqueous, and it inhibited electroshock in mice, lengthened drug-induced sleep in mice, and was safer at low doses (LD50 954.9 2.86 mg/kg body weight). It was also more effective against generalised seizures than partial ones. Fixed anticonvulsant action was observed in the roots of *A. senegalenesis*, and it was determined that there was a reasonable pharmacological basis for the nearby people to use the same for this purpose.

4. ***Acorus calamus*:** Araceae is the family that includes *Acorus calamus L*. We call it a lovely flag most of the time. Native to India, the Himalayas, and Central Asia, it is a perennial herb. It promotes hunger and facilitates stomach emptying. Fever, stomachaches, and colic are among conditions for which it is utilised. Amenorrhoea, dysmenorrheal, helminthiasis, flatulence, nephropathy, memory, and IQ are all improved by it. Given ethanolic Acorus calamus Rhizome (EEACR) at 250 mg/kg and 500 mg/kg in a MES-induced seizure paradigm, the treatment group saw a substantial decrease in hind limb extension and tonic flexion of the forelimbs ($p<0.001$) in comparison to the control group (23).

5. ***Canna Indica*:** The family Cannaceae includes *Canna Indica*. It is frequently used to treat a wide range of ailments in conventional medicine. It was distributed all across the tropics and subtropics, but mostly in the western part of the hemisphere. It grows well in flower gardens. Diarrhoea and dysentery are avoided and malaria is treated. It was applied topically to treat fever, indigestion, and as a diuretic (30)

Through its targeting of voltage-gated Na+ channels, *Canna indica L*. extract may reduce the length of tonic hind leg extension in seizures triggered by electroshock. Seizures were less frequent and had lower thresholds when the GABAergic system, glutaminergic mechanism, and Na+/Ca+ channels were all stimulated. It is yet unknown exactly what active principle and mechanism these extracts use to exert their effects (31).

6. ***Butea monosperma*:** The plant family Fabaceae includes *Butea monosperma* (Lam.). Generally speaking, it's called Kuntze. It has purifying, diuretic, aphrodisiac, and astringent properties. It encourages menstrual flow as well as diuresis. Additionally, it is applied as an antivenom for snake bites. Through either directly activating GABA receptors or increasing its impact on GABAA receptors, the extract improved GABA-mediated synaptic inhibition, delaying the onset of pentobarbital-induced sleep. The potential for improving sleep was demonstrated by the extract of *Butea monosperma*, which at 300 mg/kg considerably enhanced total sleep time. The extract may influence GABAergic neurotransmission, as evidenced by its capacity to stop PTZ-induced convulsions. In order to determine which anticonvulsant medications are effective against myoclonic and absence seizures, the PTZ test is evaluated. However, the fact that *Butea monosperma* can reduce the duration of a tonic-clonic convulsion in the MES test indicates that it works against generalised tonic-clonic convulsions(29).

7. ***Biophytum sensitivum*:** The Oxalidaceae family of plants includes *Biophytum sensitivum (L.).* Typically, tropical areas are home to this herb. Tropical Africa and Asia are among the warmer places where it can be found. It is utilised to treat a variety of conditions, including hypoglycemia, inflammatory illnesses, diabetes, phthisis, asthma, immunological modulation, apoptotic activity, chemo-protective cell-mediated immune response, hypocholesterolemia, prostaglandin biosynthesis-related tumour activity, antibacterial activity, and antioxidant activity. It functions as an antioxidant to potentially lessen the development of free radicals and inhibits the formation of prostaglandins. Pentylenetetrazol-induced tonic-clonic convulsions in mice were postponed and tonic hind limb extension was considerably reduced by B. sensitivum extract in both trial models. At 200 mg/kg, all the animals in this trial were protected. The extract's sterol and flavonoid concentration may be responsible for its anticonvulsant effects. The ethanolic leaf extract from *Biophytum sensitivum L.* has been shown to be effective in treating absence, clonic, and tonic seizures (28).

8. ***Phyllanthus amarus*:** The Euphorbiaceae family includes *Phyllanthus amarus*. In cultivation and wastelands all over the tropics and subtropics, this plant is frequently found growing as a weed. A common weed in India is *Phyllanthus amarus*. Its potent antioxidant properties have been linked to its anti-inflammatory, anti-nociceptive, anti-hyperglycemic, and anticarcinogenic properties.(32, 33) Because it prevents MES-induced hind limb extension and postpones the latency of PTZ-induced seizures, *P. amarus* may have anticonvulsant effects when combined with ethanolic and aqueous extracts through non-specific mechanisms. The aqueous and ethanolic extracts of the leaves and stems of *P. amarus* (70 mg/kg, p.o.) considerably (p0.001) finished the hind limb extension that MES had induced. Protecting the animals was the same dose, which was equally significant (p0.001).

9. ***Ocimum sanctum:*** The Lamiaceae family includes *Ocimum sanctum*. It is sometimes referred to as holy basil or tulsi, a word meaning "one, comparable." *Ocimum sanctum* is highly prized in Indian traditional medicine and Ayurveda due to its medicinal properties. (34) In addition to promoting internal physiologic balance, tulsi guards the body from damage caused by toxins (35). It has anti-inflammatory, anti-oxidant, immunological modulatory, hepatoprotective, anti-cancer, anti-asthmatic, anti-diabetic, anti-fertility, and anti-stress properties.

10. ***Cocos nucifera L***: Rats treated with OS extracts (4.25 and 8.5 mg/kg) showed a substantial decrease in THLE in the paradigm of seizures caused by MES. Medication that blocks voltage-gated Na+ channels, such as felbamate, which blocks N-methyl-D-aspartate receptors, and medications like phenytoin and carbamazepine, stop seizures caused by MES. The anticonvulsant component of OS extract is evident in its ability to prevent or halt the progression of seizures within the brain, as demonstrated by its ability to protect against THLE(36).

11. ***Catharanthus roseus*:** Apocynaceae is the family that includes *Catharanthus roseus*. Another name for it is vinca. It's a herbaceous plant that grows to a height of 1 metre and is an evergreen suburb (37). Approximately 100 distinct terpenoid indole alkaloids are produced by it. (39) The terpenoid indole alkaloids 38, which combat cancer, are sourced commercially from this source. It was used to cure coughs, wasp stings, nosebleeds, sore throats, mouth ulcers, and bleeding gums in addition to its other uses as an astringent and diuretic. Given that the roots of *Catharanthus roseus* are the source of all of the constituents listed above, the anticonvulsant activity of *Catharanthus roseus* petroleum ether extract at a dose of 400 mg/kg results in a significant reduction in the length of the extensor, clonus, and stupor phases when compared to the control group (37).

12. ***Citrus sinensis:*** In the Rutaceae family, *Citrus sinensis* belongs. There's another name for it: sweet orange. All around the world, it was extensively grown.Several chemicals are extracted from *C. sinensis* leaves, including glycosides, flavonoids, hesperidin, diosmin, triterpene, lineman, and ruteosides. Neurological disorders are treated using it. Additionally sedative effects of the methanolic extract. It has hypotensive, diuretic, analgesic, and anti-inflammatory properties. (39). Within the Rutaceae family (41), citrus comprises about 162 species. 100 mg/kg of the hydroethanolic *citrus sinensis* leaf extract was more effective than 50 mg/kg as an anticonvulsant. Which drugs are very good at avoiding seizures can be ascertained by using the convulsions caused by pentylenetetrazole. Epilepsy is largely caused by GABA;

research indicates that whilst GABA-ergic neurotransmission increases the risk of seizures, reducing GABA-ergic neurotransmission or movement might promote and facilitate seizures. By increasing the concentration of GABA, an inhibitory neurotransmitter in the central nervous system, citrus sinensis leaf extract hydroethanolic may be having an anticonvulsant effect (40).

13. ***Desmodium triflorum* :** The plant family Fabaceae includes *Desmodium triflorum* (L.). Plant in question is perennial.It is a plant that grows in all tropical nations. As an antispasmodic, sympathomimetic, central nervous system stimulant, curare-mimetic action, diuretic, galactagogue, and treatment for diarrhoea and convulsions, among other uses. Anticonvulsant effects were observed in the ethanolic extract. Lowering the duration of the convulsion and delaying its onset greatly were the effects of EEDT dosages of 400 and 800 mg/kg2. Seizures have been observed to decrease with decreasing GABAergic neurotransmission and to rise with its increase. Phenobarbitone and diazepam, the conventional anticonvulsant drugs, have been shown by multiple authors to characterise their anticonvulsant properties by augmenting GABA-mediated inhibition (44), which suggests that they should shield mice against PTZ-induced seizures.

14. ***Datura metel:*** Member of the Solanaceae family, *Datura metel* L., also known as "Datura". A 1.8-meter-tall perennial plant. East Asia is home to it. In Bangladesh, traditional herbal medicine makes use of it. Ayurvedic medicine uses D. metal seeds to treat skin rashes, diabetes, pneumonia, ulcers, and jaundice. In Brazil, calming tea is made from seeds, while cigarettes made from dried flowers are smoked (42). The extract may have its anticonvulsant effect through boosting GABA neurotransmission, as evidenced by the fact that it suppressed convulsions caused by these medications. When used in higher dosages, diazepam and other benzodiazepine-like anticonvulsants that increase GABA neurotransmission function as myorelaxants, neurotoxic agents, or anxiolytics *Datura metel* extract administered in an ethanolic solution significantly (p0.001) protects Swiss albino mice from convulsions caused by PTZ and MES. Based on central processes (43), the study found that Datura metel leaves had anticonvulsant properties.

15. *Aegle marmelos*: *Aegle marmelos* belongs to the family Rutaceae. It is used to treat analgesia, hepatitis, hypoglycemia, fever, and inflammation. Mice were administered *Aegle marmelos* extract at doses of 100 and 200 mg/kg. The Extract showed protective action against PTZ-induced seizures and disrupted MES-induced hind limb tonic extensions (HLTE) at a dose of 200 mg/kg. Because MES and PTZ block GABA's ability to act at GABA-A receptors, they may result in seizures. Gamma-aminobutyric acid is the primary inhibitory neurotransmitter implicated in epilepsy. Convulsions will decrease and rise in response to GABA neurotransmission enhancement and prevention, respectively. It has been shown that the common antiepileptic drug diazepam works by enhancing GABA-mediated inhibition in the brain. In this study, diazepam may have exacerbated MES and PTZ convulsions by GABA neurotransmission (28)

CONCLUSION:

Many different illnesses have long been treated using herbal treatments. This review showed that thirty herbs have antiepileptic characteristics. Mostly reliant on the epileptic activity of plants, herbal remedies have shown good anticonvulsant efficacy and little toxicity in the animal model at the utilised levels. More investigation is still needed for efficacy and safety aspects. This review aims to aid in the development of new herbal drugs that prevent epileptic activity by providing an overview of the antiepileptic qualities of traditional medicinal herbs. However, it is safe to state that herbal remedies have greatly contributed to the development of certain outstanding medications. Hence, it has been concluded that herbs have a great potential to treat epilepsy and by using antiepileptic herbs we can formulate and develop a polyherbal antiepileptic formulation.

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