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Anti-Epileptic Indian Medicinal Plants: A Comprehensive Review on their Ethnopharmacological Perspectives of Recent Advancement

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ABSTRACT: The study explores the potential of Indian medicinal plants as botanical treasures for managing epilepsy. Epilepsy, a neurological disorder characterized by recurrent seizures, poses a significant global health challenge. Traditional medicinal practices in India have a rich history of incorporating various plant-based remedies for neurological ailments, including epilepsy. The data was collected from various scientific databases like Google Scholar, Science Direct, Elsevier, Springer and Pubmed. The collected data includes the following details - Plant part used, dose and type of extract, reference and inducing drug used and the mechanism of actions. The article thoroughly examines the phytochemical constituents found in Indian medicinal plants, elucidating their neuroprotective and anticonvulsant properties and their scrutinized bioactive compounds and therapeutic potential. The review integrates findings from preclinical and clinical studies, shedding light on the mechanisms of action and safety profiles of these plant-derived compounds. The conclusion of the manuscript emphasizes the promising role of Indian medicinal plants in epilepsy management. The identified botanical treasures offer a holistic and potentially sustainable approach to complement existing antiepileptic medications. The reviewed evidence underscores the need for further research, clinical trials, and integration of traditional knowledge into mainstream healthcare for the development of effective and accessible treatments for epilepsy. By recognizing the botanical wealth embedded in Indian traditional medicine, this review advocates for a paradigm shift toward harnessing nature's gifts in the pursuit of enhanced epilepsy care.

1. INTRODUCTION

In a condition known as epilepsy, a network of neurons or nerve cells in the brain suddenly malfunction, generating abnormal emotions, sensations, or muscle spasms (Rabiei, 2017). Epileptic seizures can occur for a variety of reasons, including genetic, developmental, or acquired factors. There are around 50 million individuals with epilepsy disorder all over the world (Fisher et al., 2005). Schizophrenia and epilepsy can coexist, and seizures can include convulsions, loss of consciousness, and uncontrollable movements. It is a psychiatric disorder that affects young adults and adolescents frequently. Also, a number of the physical and mental signs of schizophrenia overlap with those of epilepsy, making it more challenging to identify and manage epilepsy in persons who suffer from it (Naoto & Masumi, 2022). Epilepsy has been associated with an array of distinct illnesses including autoimmune diseases, metabolic abnormalities, infection in brain and acute injuries to the brain such as strokes, brain tumors, or condition epilepticus (Scheffer et al., 2017; Zahiruddin et al., 2020).

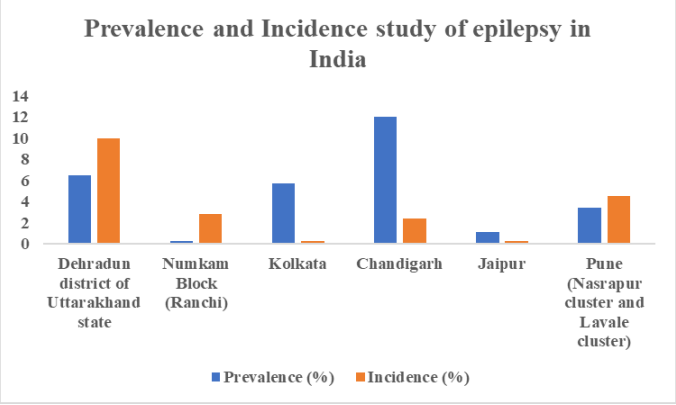

Figure 1. Prevalence and Incidence study of epilepsy in India from 2007 to 2021.

According to the World Health Organization 50 million of peoples have epilepsy condition around the world. Every

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Table 1
Prevalence and incidence study of epilepsy in India.

S.No	Year	Place of Survey	Total No. of Cases	Epilepsy affected Cases	Prevalence (%)	Incidence (%)	References
1.	2007	Dehradun district of Uttarakhand state	14086	141	6.5	10	Goel et al. (2011)
2.	2009	Numkam Block (Ranchi)	114068	318	0.28	2.78	Nizamie et al. (2009)
3.	2010	Kolkata	52377	309	5.7	0.27	Banerjee et al. (2010)
4.	2014	Chandigarh	3684	1825 in urban area 1859 in rural area	12	2.4	Pandey et al. (2014)
5.	2019	Jaipur	344802	380	1.1	0.22	Panagariya et al. (2019)
6.	2021	Pune (Nasrapur cluster and Lavale cluster)	75455	19181	3.44	4.5	Srivastava et al. (2021)

year, 5 million people are estimated to experience epilepsy worldwide. Epilepsy is predicted to be reported in 49 out of 100,000 individuals annually in high-income countries while this percentage can increase (139 per one million) as well as nearly 80% of people with epilepsy live in areas with low and middle economic levels (https://www.who.int/news-room/fact-sheets/detail/epilepsy). Fifty million people globally have epilepsy, including 10-12 million instances in India (Garg, 2020). In India, there are almost 1.5 million women with epilepsy who are of childbearing age, making up 1/6th of all women with epilepsy worldwide. Fifty-two percentage of them are in the age group of 15 to 49. For women with epilepsy, reproductive difficulties are a crucial factor to take into account (Thomas, 2011). According to recent reports, about 1-2% of the total Indian population has schizophrenia and 5% of Indians have common mental diseases including anxiety, depression and epilepsy (Mishra et al., 2011). However, in many cases the motivation underlying seizures is unexplained. Furthermore, epilepsy patients frequently exhibit neurological dysfunctions such as memory loss, anxiety, sadness, and mental morbidity like autism spectrum disorders, all of which have significant adverse effects on the general wellness of the patients (Mohseni-Moghaddam et al., 2021).

In a healthy brain, excitatory and inhibitory impulses are balanced. During an epileptic seizure, this balance disrupts, causing neurons to fire abnormally. When confined to a small area without symptoms, it's called interictal epileptic distortion. The diverse nature of epilepsy complicates understanding, but these disruptions can cause seizures affecting consciousness, movement, perception, behavior, and autonomic functions (Adassi et al., 2023).

For determination of onset and progression of seizures, no studies have specifically explored the anatomical abnormalities associated with epilepsy. It is hypothesized that hypersynchronous neuronal activity in the epileptic brain is facilitated by alterations in neurological function. These changes may involve modifications in synaptic function, such as the release of neurotransmitters or the expression of neurotransmitter receptors, as well as alterations in intrinsic excitability mechanisms, including ion channel conductivity, second messenger systems, or protein synthesis. Additionally, aberrant activation and proliferation of microglia and astrocytes may disrupt brain function, leading to increased excitability and seizures. This suggests that maintaining neuronal equilibrium and the integrity of the blood-brain barrier (BBB) is crucial for proper brain function. Disruption of the BBB and subsequent leakage could promote excitability by inducing inflammation in the brain (Raedt et al., 2018).

Phytoconstituents in medicinal plants possess catalytic and synergistic properties, enabling them to treat various diseases. While antiepileptic drugs help 60-70% of patients reduce seizures, they do not address underlying causes and have unavoidable side effects and high costs. Herbal and traditional Ayurvedic treatments are widely used for neurological conditions like epilepsy, depression, Parkinson's disease, Alzheimer's, anxiety, schizophrenia, and neurotoxicity. These natural remedies offer a promising alternative, potentially minimizing side effects and costs associated with conventional drugs, while effectively managing symptoms and improving patient outcomes in various neurological disorders (Beghi, 2020; Faheem et al., 2022). This review offers comprehensive information on the traditional and modern use of medicinal plants in managing epilepsy. It serves as an effective platform to validate the dataset and enhance the credibility of medicinal plants such as *Punica granatum* L. *Carissa edulis* (Root Bark), *Citrullus colocynthis* (Fruit Pulp), *Prosopis cineraria* (Stem Bark), *Cardiospermm halicacabun* (Root), *Bunium perscicum* (Dried seeds), *Teucrium polium* (Dried aerial parts) etc., for their ethnopharmacological potential. By integrating historical and contemporary perspectives, the review underscores the significance of these plants in epilepsy treatment, promoting further research and application. This holistic approach aims to bridge the gap between traditional knowledge and modern science, ensuring a robust understanding of the efficacy and safety of medicinal plants in epilepsy management, ultimately benefiting both researchers and patients.

Table 2
Modern drugs used in treatment of Epilepsy.

S.No.	Drug	Source	Class	Mode of Action	Associated Adverse effects	References
1.	Cannabinoid	*Cannabis* genus	CNS Stimulant	Generate analgesic by inhibiting in brain and spinal cord, which transmit pain via a G-protein pathway.	Mild euphoria, hypertension, hypokalemia	Cohen and Weinstein (2018)
2.	Gabapentin		Anticonvulsant	Inhibit Gabapentin neurotransmitter	10% side effect reported in gabapentin and 11% in lamotrigine	Crawford et al. (2001)
3.	Levetiracetam	Pyrrolidinone and carboxamide	Anticonvulsant	Levetiracetam's mode of action is not well understood. However, based on clinical experience, For the treatment of focal seizures, possibly also generalized epilepsy, levetiracetam appears to be a well-tolerated and very successful medication.	Anxiety, deep or fast breathing, headache, drowsy etc.	Ben-Menochem (2003)
4	Curcumin	*Curceuma longa*	Anti-inflammatory	release serotonin and dopamine increase neurotrophic compounds levels in brain neurotrophic factors (BDNF)	Gastric ulceration, hyperplasia, according to various studies, curcumin promotes alterations in DNA and dependent on dosage chromosomal disruptions in cell lines from mammals when administered dose of 10 mg/ml.	Bhat et al. (2019); Wang et al. (2008)
5	Morin hydrate	Moraceae family	Flavanol Anti-oxidant Anti-inflammatory	Increase brain monoamines, brain derived neuroprotective factor (BDNF)	Nausea, Vomiting, Stomach pain	Rajput et al. (2021)
6	Clobazam	7-Chloro-1H-1,5-benzodiazepine-2,4(3H,5H)-dione	Benzodiazepine, Anticonvulsant	The primary mechanism of action is thought to involve binding to the benzodiazepine receptor on GABA Channels which modulates gamma-aminobutyric acid (GABA) induced chloride influx.	Ataxia, fatigue, somnolence, insomnia etc.	Kilpatrick (2011)

Continued on next page

Table 2 continued

S.No.	Drug	Source	Class	Mode of Action	Associated Adverse effects	References
7.	Felbamate	Carbamate ester	Antiepileptic drugs	Inhibition of N-methyl-D-asparate receptor and action on gamma amino butyric acid receptor.	Vomiting, Insomnia. Headache, dizziness etc.	White (2011)
8.	Perampanel	-	Anticonvulsant	Perampanel inhibits the AMPA receptor (α-amino-3-hydroxy-5-mrthyl-4isoxazole propionic acid) non-competitively to reduce neuronal excitement.	Dizziness, somnolence, fatigue, headache etc.	Löscher et al. (2013)
9.	Vigabatrin	Gamma-amino acid	Anticonvulsant	It decreases GABA-transaminase (GABA-T) action, raising the brain's levels of this inhibitory neurotransmitter.	Diarrhea, dizziness, eye pain, joint pain etc.	Willmore et al. (2008)
10.	Lamotrigine	Phenyltriazine class	Antiepileptic (Phenyl triazine)	It acts by blocking the opening of voltage-gated sodium channels, which in turn inhibits the release of excitatory amino acids, mainly glutamate.	Dizziness, ataxia, nausea, vomiting etc. Czuczwar (2010)	
11.	Tiagabine	Nipecotic acid	Anti-convulsant	By inhibiting the GABA transporter GAT 1, it specifically affects glial and neuronal GABA absorption in the central nervous system. Increased intra-synaptic GABA concentrations brought on by GAT 1 blockage result in increased inhibitory signals being transmitted by neurons.	Nervousness, depression, dizziness, asthenia etc.	Lasoń et al. (2011)
12.	Oxcarbazepine	5H-dibenz[b,f]azepine and phosgene	Anticonvulsant	It acts by blocking voltage-gated sodium channels and stabilizing membranes.	Fatigue, sedation, rashes, dizziness etc.	Lasoń et al. (2011)
13.	Topiramate	Monosaccharide d-fructose	Anticonvulsant	It enhances GABA efficacy to activate GABA-A receptors then it blocks the AMPA glutamatergic receptors and reduces voltage-gated sodium currents.	Somnolence, headache	Lasoń et al. (2011)
14.	Zonisamide	Sulfamoylmethyl substituent	Sulphonamide Antiepileptic drugs	It acts by blocking repetitive firing of voltage-gated sodium channels. It is a inhibitor of t-type calcium channels.	Abnormal thinking, Dizziness, somnolence, confusion etc.	Schulze-Bonhage (2010)

2. PREVALENCE AND INCIDENCE OF EPILEPSY

India is a vast developing country with limited resources that serves approximately 17.76% of the global population (https://www.worldometers.info). In India, neurological illnesses, both fatal and non-fatal, are among the leading causes of noncommunicable and communicable disease burden Epilepsy is among the most widespread neurological disorders in the world.

Epilepsy is the foremost neurological disorder affecting one in every 26 individuals affect over 1% of Americans which control and prevent disease. According to the WHO, 49 out of every 100,000 people in high-income nations suffered from an epilepsy being diagnosed, compared to 139 people in low- and middle-income countries. Epilepsy impacts 0.2-0.6 per 1,000 individuals in India and 3.0-11.9 per 1,000 persons on a yearly basis, respectively. There are many factors that might affect a person's quality of life (QOL), and these factors may have a big impact on their physical, mental, social, and cognitive well-being (Gowda et al., 2022). The prevalence and incidence study of epilepsy in India from 2007 to 2021 has been summarized in Table 1 and Figure 1.

3. MANAGEMENT OF EPILEPSY

It is crucial to remember that epilepsy can not be cured, and there is always a risk of experiencing another seizure. About 80 percent of people with epilepsy can successfully manage their seizures with treatment and certain types of surgeries. While epilepsy can affect anyone, it typically develops in young individuals, often between the ages of 5 and 20. People with epilepsy frequently have a family history of seizures. Seizures can sometimes be triggered by unfavorable circumstances. For instance, a high fever can cause a seizure even when the person is on medication to manage epilepsy. Seizures can also be triggered by abnormal salt levels, blood glucose, or certain drugs. To support a clinical diagnosis, temporal lobe and interictal EEG waves should be investigated; however, multiple EEGs may be necessary. If epileptiform activity is absent in approximately three EEGs, a reassessment of the diagnosis is warranted.

An MRI scan is essential to determine the type, class, and origin of the abnormality. Medications commonly used include topiramate, lamotrigine, phenytoin, and carbamazepine (Warren & Blume, 2003) . Antiepileptic medications may not be effective for treating temporal lobe epilepsy. The need for a second medication, either as monotherapy or as multiple therapy, indicates the severity of the condition and reduces the likelihood of successful management. In such cases, epilepsy treatment requires careful attention. Diagnosing this benign condition is challenging without the presence of typical "rolandic" spikes on an EEG of an unsedated patient, whether awake or asleep, often necessitating repeated EEGs to confirm abnormalities. If such findings are absent, the diagnosis becomes doubtful, requiring further testing, including neuroimaging. Ninety-eight percentage of the time, the ability to have seizures ends by adolescence, allowing for the discontinuation of medication. If the seizures are infrequent and do not interfere with the child's activities, therapy may not be necessary (Bhakuni et al., 1988). Several modern drugs have been used for treatment of epilepsy (Table 2).

4. MEDICINAL PLANTS USED IN BRAIN DISORDERS

The necessity of medicinal plants in addressing brain disorders has garnered increasing attention within the scientific and medical communities. The rich biodiversity of plant species offers a vast array of bioactive compounds that exhibit therapeutic potential for managing various neurological conditions. As conventional pharmacological interventions often come with side effects and limited efficacy, the exploration of medicinal plants provides a promising avenue for novel treatments. Medicinal plants are replete with phytochemicals, such as alkaloids, flavonoids, terpenoids, and polyphenols, known for their neuroprotective properties. These compounds interact with biological systems, modulating cellular pathways and exhibiting antioxidant, anti-inflammatory, and anti-apoptotic effects. Such multifaceted actions play a pivotal role in mitigating the complex pathophysiology of brain disorders (Gaurav et al., 2022, 2023; Salar et al., 2023; Zahiruddin et al., 2020).

The role of medicinal plants in disorders like Alzheimer's, Parkinson's, and epilepsy is particularly noteworthy. Plants like *Ginkgo biloba*, with its flavonoids and terpenoids, have shown potential in improving cognitive function and slowing neurodegeneration. Turmeric (*Curcuma longa*) and its active compound, curcumin, exhibit anti-inflammatory properties that may alleviate symptoms associated with brain disorders. Additionally, the anticonvulsant properties of plants like *Valeriana officinalis* highlight their potential in epilepsy management. Crucially, medicinal plants not only address symptoms but also offer neuroprotection, potentially slowing the progression of certain brain disorders. The holistic nature of these plant-based interventions aligns with the growing emphasis on personalized and integrative medicine in neurological care (Basist et al., 2022; Gaurav et al., 2023; Gautam, 2022; Insaf et al., 2022; Khan, Gaurav, et al., 2022; P. Kumar et al., 2021; Szwajgier et al., 2017). Ethnopharmacological role of medicinal plants of in management of epilepsy has been summarized in Table 3 and reported phytochemicals with their structure has been reported in Table 4 and Figure 2 and 3.

The clinical assessments and potential therapeutic benefits of various plant extracts, focusing on their effects on neurological health and cognitive function. It insights into how specific plants or their parts have been used to address conditions like neurodegeneration, cognitive decline, and sleep disorders. *Viola tricolor* (Leaves), particularly the essential oil extracted from *Viola odorata*. The essential oil contains active compounds such as 1-phenyl butanone, linalool, benzyl alcohol, α-cadinol, globulol, and viridifloro. According to Feyzabadi et al., the oil demonstrated neuroprotective properties against neurodegeneration induced by insomnia and has been shown to improve sleep quality.

Table 3
Ethnopharmacological role of medicinal plants in management of epilepsy.

S. No	Plants/Parts	Dose	Extract	Reference Drug (Positive control)	Mode of Exposure (Negative control)	Mechanism of action	References
1.	*Carissa carandas* Linn (Root)	(200, 400 mg/kg, intraperitoneally)	Ethanol	Diazepam (0.5 mg/kg, intraperitoneally) Phenobarbitone (10 mg/kg, intraperitoneally) Phenytoin (25 mg/kg, intraperitoneally)	Maximum electroshock of 50 Hz, 150 mA, administered through ocular electrode for 0.2 seconds.	It works by inhibiting the effect of GABA neurotransmitter on glutamic acid in the brain.	Hegde et al. (2009)
2.	*Pongamia pinnata* Linn. (Leaves)	(250 mg/kg, intraperitoneally)	Ethanol	Phenytoin (25 mg/kg, intraperitoneally)	Maximal electroshock of 150 mA for 0.2 sec administered through corneal electrode	It acts increasing Gama Amino butyric acid in the brain.	Manigauha (2009)
3.	*Viola tricolour* (Leaves)	(400 mg/kg, orally)	Hydro-alcohol	Diazepam (3 mg/kg, intraperitoneally) Pentylenetetrazol (100 mg/kg, orally)	Maximum electroshock delivered by an ear clip electrode at 50 Hz and 150 mA for one second. Pentylenetetrazole (100 mg/kg b wt., orally)	It acts on voltage-dependent sodium channel Inhibitors. It acts on glutaminergic receptor	Rahimi et al. (2019)
4.	*Punica granatum* L. (Seed)	(400, 800 mg/kg, orally)	Petroleum ether, Methano-lic and aqueous extract	Diazepam (3 mg/kg, intraperitoneally) , Phenytoin (25 mg/kg)	Pentylenetetrazole (80 mg/kg, intraperitoneally), Maximum electroshock delivered by an ear clip electrode at 6 Hz one second	It acts as a GABAA receptors	Viswanatha et al. (2016)

Continued on next page

Table 3 continued

5.	*Carissa edulis* (Root Bark)	Sub fraction (S1) - (150, 300, 600 mg/kg, intraperitoneally) S2 - (250, 500, 1000 mg/kg, subcutaneous)	Aqueous and ethanol fraction	Sodium valproate (200 mg/kg, subcutaneous) Pentylenetetrazole (85 mg/kg, subcutaneous) Phenytoin (20 mg/kg, intraperitoneally) Phenobarbital (30 mg/kg, intraperitoneally)	Pentylenetetrazole (85 mg/kg, subcutaneous) Maximal electro shock induced convulsion 150 pulse/sec and 80 mA for 0.6 Sec through corneal electrode. Picrotoxin (10 mg/kg, subcutaneous) N-Methyl-D-aspartate (75 mg/kg, subcutaneous) Aminophylline (300 mg/kg, subcutaneous) Strychnine (1.5 mg/kg, subcutaneous) Pridoxine (200 mg/kg, intraperitoneally) Isoniazid (500 mg/kg, subcutaneous)	It inhibiting GABA receptor channel and lowering GABAergic tone. Neurotransmitter inhibiting gamma amino butyric acid, blocks GABAergic. Neurotransmission in brain	Ya'u et al. (2008)
6.	*Citrullus colocynthis* (Fruit Pulp)	(10, 25, 50, and 100 mg/kg, intraperitoneally)	Hydro-alcoholic Extract	Diazepam (1 mg/kg, intraperitoneally) Flumazenil (2 mg/kg, intraperitoneally) Naloxone (5 mg/kg, intraperitoneally)	Pentylenetetrazole (60 mg/kg, intraperitoneally)	To enhance GABA neuro- transmission, it binds to the GABA amino butyric acid receptor.	Ya'u et al. (2008)
7.	*Prosopis cineraria* (Stem Bark)	(200, 400 mg/kg, intraperitoneally)	Methanol extract	Phenytoin (25 mg/kg, intraperitoneally)	Maximal electroshock is given 150 mA for 0.2 sec through corneal electrode in wistar albino mice.	It acts by blocking of voltage dependent sodium channels increase action of potential.	Velmurugan and Ganesan (2012)

Continued on next page

Table 3 continued

8.	*Cardiospermm halicacabun* (Root)	(30, 100, 300 mg/kg, orally)	Alcoholic Extract	Phenytoin (25 mg/kg, orally) Diazepam (10 mg/kg, orally)	Electrical current 50Hz, 60 mA is passed for 0.2 sec through ear clip electrode. Pentylenetetrazole (80 mg/kg, intraperitoneally) Picrotoxin (3.5 mg/kg, intraperitoneally) Strychnine (3.5 mg/kg, intraperitoneally) Isoniazid (300 mg/kg, intraperitoneally)	It works by enhancing GABAergic-mediated neuro-transmission and general-ized tonic-clonic and partial seizure inhibiting voltage-dependent sodium channels.	Dhayabaran et al. (2012)
9.	*Bunium perscicum* (Dried seeds)	Essential oil (0.25, 0.75, 1, 1.25 ml, 1.5 ml/kg, intraperitoneally) Methanolic Extract (0.5, 1, 1.5, 2, 3, 4 gm/Kg, intraperitoneally)	Essential oil and Methano-lic extract	Phenytoin (3 g/kg intraperitoneally)	Pentylenetetrazole (100 mg/kg, intraperitoneally) Electrical current is passed 50Hz, 50mA for 1 sec through ear clip electrode.	Inhibit excitatory neuronal transmission and blocks voltage-sensitive sodium channel.	Mandegary et al. (2012)
10.	*Teucrium polium* (Dried aerial parts)	(10, 25, 50 mg/kg b wt., intraperi-toneally)	Aqueous, ethyl acetate, chloro-form extract	Diazepam (4 g/kg, intraperitoneally)	Pentylenetetrazole (80 mg/kg, intraperitoneally) Electric current (120 V, 50 Hz) for 2 sec) through ear clip electrode	It acts by inhibiting voltage dependent sodium channel.	Khoshnood-Mansoorkhani et al. (2010)
11.	*Solanum sisymbriifolim* (Fruits)	(25, 50, 100 mg/kg, intraperitoneally)	Solasodine isolated from S. sisymbri-ifoliu	Diazepam (4mg/kg, intraperitoneally)	Pentylenetetrazole (75 mg/kg, intraperitoneally) Picrotoxin (12 mg/kg, intraperitoneally)	It acts by increasing Gama Aminobutyric acid ($GABA_A$) receptor-linked chloride ions and reduces seizures by inhibition.	Chauhan et al. (2011)

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Table 3 continued

12.	*Smilax china* (Rhizome)	(200, 400 mg/kg, intraperitoneally)	Ethanol by cold macera-tion, hexane, chloro-form and ethyl acetate	Pentobarbitone (30 mg/kg, intraperitoneally)	Pentylenetetrazole (80 mg/kg, subcutaneous) MES – Electric current of 60 mA for 0.2 sec via a corneal electrode.	It acts enhance GABA neurotransmission and reduce glutamate transmission.	Vijayalakshmi et al. (2011)
13.	*Achyranthes aspera* (Root)	(5, 10 mg/kg, intraperitoneally)	Methanolic extract	Diazepam (5 mg/kg, intraperitoneally)	Pentylenetetrazole (60 mg/kg, intraperitoneally) Picrotoxin (5 mg/kg, intraperitoneally) Bicuculline (4 mg/kg, intraperitoneally) MES - Electric current of 50 mA for 0.2 sec through crocodile ear clip pair.	It acts by increasing GABAergic neurotransmission to antagonize seizures	Gawande et al. (2017)
14.	*Ocimum sanctum* (leaf)	500 & 1000 mg/kg	Leaf extract of O. sanctum	Carbamazepine (20 mg/kg)	Pentylenetetrazole (30 mg/kg, intraperitoneally)	It acts blocking voltage dependent sodium channels by increasing the action potential.	Sachan (2023)
15.	*Lobelia nicotiana* folia (Leaves)	(10, 20, 30 mg/kg, intraperitoneally)	Lobeline isolated from leaf of L. nicotiana folia	Diazepam (3 mg/kg, intraperitoneally)	Pentylenetetrazole (90 mg/kg, intraperitoneally) Strychnine (3 mg/kg, intraperitoneally)	Drugs that directly bind and activate GABAA receptors or that have an impact on GABA production, transport, and metabolism have an anti-epileptic effect due to GABAergic inhibitory transmission.	Tamboli et al. (2012)

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Table 3 continued

16.	*Ebenus stellata, Sophora alopecuroides, Caesalpinia gilliiesii* (Aerial part)	E. stellata (7g/kg b wt. intraperitoneally) S. alopecuroides (0.2 g/kg) C. gilliesii (0.5 g/kg)	Hydro-alcoholic and aqueous extract	Phenytoin (25 mg/kg) Ethosuximide (150 mg/kg)	MES - 50 mA, 50 Hz electroshock delivered through ear clip electrode for one second. Pentylenetetrazole (60 mg/kg, intraperitoneally)	It reduces inhibitory neurotransmission mediated by GABA A receptors or glutamatergic inhibited by N-methyl-D-aspartate receptor.	Khodaparast et al. (2012)
17.	*Hypericum scabrum* L. (Aerial part)	(125, 500 mg/ kg, intraperitoneally)	Aqueous extract	Diazepam (1 mg/kg, intraperitoneally)	Pentylenetetrazole (100 mg/kg, intraperitoneally) Picrotoxin (10 mg/kg, intraperitoneally)	It works enhance the action of gamma amino butyric acid, which inhibit neuronal transmission.	Ebrahimzadeh et al. (2013)
18.	*Morus alba* (Stem bark)	(5 and 10 mg/kg, intraperitoneally)	Morusin isolated from stem bark of M. alba	Diazepam (5 mg/kg) Phenytoin (20 mg/kg)	Isoniazid (300 mg/kg, intraperitoneally) MES – 150 mA of electricity was sent through the auricular electrode for 0.2 seconds.	Voltage-gated sodium channels block by opening and excitatory neuro-transmitter glutamate releases lower.	Gupta et al. (2014)
19.	*Fumaria schleicheri* (herb)	F. scheicheri (100 mg/kg) Flavonoid fraction (0.05, 0.5 mg/kg) Alkaloid fraction (0.2 mg/kg) Protopine fraction (0.005, 0.05 mg/kg)	Aqueous extract of above ground parts of F. scheicheri and Protopine fraction	Sodium valproate (300 mg/kg)	Pentylenetetrazole (80 mg/kg, intraperitoneally)	Isoquinoline alkaloid fraction suppress the glutamate excitatory neurotransmitter by inhibition of calcium ions influx. Protein polysaccharide fraction inhibit glutamate receptors and interleukin-1 β pathway.	Prokopenko et al. (2016)

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Table 3 continued

20.	*Buddleja polystachya* (Leaf)	(100, 200, 400 mg/kg)	Methanol extract	Sodium valproate (200 mg/kg) Phenytoin (25 mg/kg) Diazepam (5 mg/kg)	Pentylenetetrazole (85 mg/kg subcutaneous) MES- Mice are exposed to 50-mA electric current through an ear-clip electrode for 0.2 seconds by an electro-convulsometer.	It acts to inhibit T-type calcium currents while boosting GABAergic neurotransmission.	Agedew et al. (2021)
21.	*Ginkgo biloba* (Leaf)	100 mg/kg	Ethanolic extract	L-carnitine (300 mg/kg)	Pentylenetetrazole (40 mg/kg, intraperitoneally)	It acts enhance Gama Amino butyric acid (GABA) pathway at $GABA_A$ receptor	Essawy et al. (2022)
22.	*Caralluma dalzielii* (Aerial Parts)	(250, 500 and 1000 mg/kg orally)	Aqueous extract	Diazepam (5 mg/kg) Phenytoin (25 mg/kg)	Pentylenetetrazole (90 mg/kg, intraperitoneally) Strychnine (2.5 mg/kg, intraperitoneally) MES – Electric current of 60 mA of 60 Hz for 2 sec. through corneal electrode	It acts enhance Gama Amino butyric acid (GABA) pathway at $GABA_A$ receptor inhibits neurotransmitter	Ugwah-Oguejiofor et al. (2023)
23.	*Syzygium aromaticum* (Dried Flower buds)	(5, 10, 15, 20 mg/kg, intraperitoneally)	Methanol extract	Clonazepam (1 mg/kg, intraperitoneally) Diazepam (3 mg/kg, intraperitoneally)	Pentylenetetrazole (70 mg/kg, intraperitoneally) Picrotoxin (7.5 mg/kg, intraperitoneally) Bicuculine (4 mg/kg, intraperitoneally)	A significant inhibitory neurotransmitter termed bicuculline (BICU) is effective directly on postsynaptic GABAA receptors, whereas pentylenetetrazole functions through Gamma Amino Butyric Acid (GABA) pathway increases receptor for GABAA.	Lina et al. (2023)
24.	*Ascotheca paucinervia* (Leaves)	(250, 500 mg/kg)	Aqueous Extract	Diazepam (10 mg/kg, orally)	Strychnine (2.5 mg/kg, intraperitoneally)	It acts inhibit release Glutamate excitatory neurotransmitter	Judicaël et al. (2023)

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Table 3 continued

25.	Pheophytin A Spinach (Leaves)	(20 mg/kg b wt., intraperi-toneally)	Pheophytin A is isolated from Spinach leaves by column chro-matogra-phy	Sodium valproate (300 mg/kg, intraperitoneally)	MES – Maximal electric shock of 79 mA for 0.2 sec through corneal electrode	It acts GABA (Gama amino-butyric acid) level in brain and block voltage gated sodium channel	Almuthaybiri et al. (2023)
26.	*Anopyxis klaineana* (Stem bark)	10, 30 or 100 mg/kg, orally	Methanolic Extract	Diazepam (0.1, 0.3 or 1.0 mg/kg, intrapertoneally)	PTZ – 85 mg/kg subcutaneously	Inhibit Gama amino butyric acid on neuronal transmission	Biney et al. (2023)
27.	*Lycium schweinfurthii* (Leaves)	(400 mg/kg, intraperi-toneally)	Methanol extract	Diazepam (5.0 mg/kg, orally) Flumazenil (2.0 mg/kg, orally)	Picrotoxin (5.0 mg/kg, intraperitoneal)	It enhances chloride ions channel connected to GABA-A receptor	Biney et al. (2023)
28.	*Diospyros peregrine* (Root)	(400 mg/kg, orally)	Cold macera-tion, methanol extract	Diazepam (4 mg/kg, intraperitoneally)	Isoniazid (300 mg/kg, intraperitoneally) Pilocarpine (240 mg/kg, intraperitoneally)	It acts enhance $GABA_A$ receptor mediated inhibition	Mia et al. (2023)
29.	*Malvaviscus arboreus* (Flowers, leaves, stem and root)	(122.5, 245, 490 mg/kg)	Aqueous lyophilized extract	Clonazepam (0.1 mg/kg)	Picrotoxin (7.5 mg/kg, intravenous) Strychnine (2.5 mg/kg, intravenous) Pilocarpine (350 mg/kg, intravenous) Pentylenetetrazole (70 mg/kg, intravenous)	It acts by enhance the inhibitory action of Gama amino butyric acid on neuronal transmission or it acts by inhibit release of Glutamate excitatory neurotransmitter	Adassi et al. (2023)

Continued on next page

Table 3 continued

30.	*Ipomoea asarifolia* (Leaves)	(50, 300, 600 mg/kg, intraperitoneally)	Chloroform, butanol, hexane, ethanol fraction extract Residual Aqueous fraction (RAF) (75 mg/kg b wt., intraperitoneally)	Sodium valproate (200 mg/kg b wt., intraperitoneally) Phenytoin (20 mg/kg, intraperitoneally) Flumazenil (2 mg/kg, intraperitoneally) Diazepam (2 mg/kg, intraperitoneally) Strychnine (1 mg/kg, subcutaneous) Ketamine (5 mg/kg, intraperitoneally)	Pentylenetetrazole (85 mg/kg, subcutaneous) MES – Electric current of 50 mA for 0.2 sec through ear clip electrode given to mice by using electro-convulsometer.	It acts by inhibiting voltage gated sodium channels and it also binds with $GABA_A$ receptor in rat's brain and inhibit NMDA receptor mediated epileptic discharge	Chiroma et al. (2022)
31.	*Lactuca serriola* (Seeds)	(300, 400, 500 mg/kg, b wt.)	n-hexane, chloroform, methanol and distilled water extract	Diazepam (1 mg/kg, orally) Phenobarbitone (2 mg/kg b wt., intraperitoneally)	Strychnine (5 mg/kg, intraperitoneally) Picrotoxin (5 mg/kg, intraperitoneally) Pentylenetetrazole (35 mg/kg, intraperitoneally)	It acts by opening GABA activated chloride ion channels to increase $GABA_A$ action	Ullah et al. (2022)
32.	*Coccinia grandis* (Leaf)	(200, 400 mg/kg, intraperitoneally)	Hydro-ethanolic extract	Diazepam (2 mg/kg, intraperitoneally)	Pentylenetetrazole (80 mg/kg, intraperitoneally) MES- Electroshock of 50 mA for 0.2 sec through ear clip Isoniazid (300 mg/kg, orally)	It acts by increase GABA mediated opening channel of chloride ions of $GABA_A$ receptor which decreases the epileptic activity in brain	D.P. Kumar and Kumar (2022)
33.	*Ficus platyphylla* (Stem bark)	(400 mg/kg)	Flavonoid rich fraction of F. platyphylla stem bark hydro-ethanolic extract	Diazepam (2 mg/kg, intraperitoneally)	Pentylenetetrazole (80 mg/kg, intraperitoneally)	It acts enhance inhibitory action of Gama amino butyric acid on neuronal transmission or it also acts by inhibit release of Glutamate excitatory neurotransmitter	Hassan et al. (2022)

Continued on next page

Table 3 continued

34.	*Decalepis nervosa* (Root)	(250, 500 mg)	Aqueous extract	Diazepam (2 mg/kg, intraperitoneally)	Pentylenetetrazole (80 mg/kg, subcutaneous) Isoniazid (300 mg/kg, subcutaneous)	It acts by enhancing the neuronal transmission. Inhibiting effect caused by Gamma amino butyric acid.	Das et al. (2022)
35.	*Pentas schimperiana* (Root bark)	(100, 200, 400 mg/kg b wt. of extract)	Methanolic extract	Sodium valproate (200 mg/kg, subcutaneous) Phenytoin (25 mg/kg, subcutaneous)	Pentylenetetrazole (85 mg/kg, subcutaneous) MES- Electric current of 50 mA for 0.2 sec is passed through ear clip.	It acts reduce T-type calcium channel and enhance GABAergic neurotransmission.	Fisseha et al. (2022)
36.	*Biophytum umbraculum* (Root)	(100, 200, 400 mg/kg)	Hydro-alcohol extract	Phenytoin (25 mg/kg, orally) Valproic acid (200 mg/kg, orally)	Pentylenetetrazole (85 mg/kg, subcutaneous) MES- Electric current of 50 mA for 0.2 sec is passed through ear clip.	It acts reduce T-type calcium channel and enhance GABAergic neurotransmission.	Fisseha et al. (2022)
37.	*Valeriana edulis* (Roots)	(100 mg/kg, intraperi-toneally)	Ethanol extract	Ethosuximide (100 mg/kg, intraperitoneally)	Pentylenetetrazole (35 mg/kg intraperitoneally)	It works by boosting the inhibition of neuronal transmission caused in Gamma amino butyric acid.	González-Trujano et al. (2021)
38.	*Lantana camara* (Stem, Flower)	(200, 400 mg/kg, orally)	Ethanolic, aqueous extract	Phenytoin (25 mg/kg, intraperitoneally) Diazepam (4 mg/kg, intraperitoneally)	MES – Electric current of 45 mA for 0.2 sec through corneal electrode. Phenobarbitone (30mg/kg, intraperitoneally)	It works by enhancing amount of GABA in the brain while inhibiting GABA transaminase.	Bora and Singh (2019a)
39.	*Morinda lucida* (Leaves)	(200, 400, 800 mg/kg, orally)	Cold macera-tion methanol extract	Diazepam (0.5 mg/kg, intraperitoneally)	Pentylenetetrazole (80 mg/kg, intraperitoneally) Isoniazid (5 ml/kg, orally)	Inhibited GABA A neurotransmitter receptor in brain	Estella et al. (2020)

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Table 3 continued

40.	*Morus nigra* (Fruits)	(125, 250, 500 mg/kg, orally)	Methanol extract	Diazepam (5 mg/kg, orally)	Strychnine (1 mg/kg)	Inhibiting glycine to glycine-gated chloride channel, neurotoxin (strychnine) stimulates the spinal cord. Once it binds to this channel, it inhibits the transmission of nerve signals, increasing the influx of chloride ions and causing cell hyperpolarization.	Zehra et al. (2021)
41.	*Calotropis procera* (Fresh leaf)	(100, 300 mg/kg, orally)	Hydro-ethanolic extract	Diazepam (0.1–1.0 mg/kg, intraperitoneally) Strychnine nitrate (0.5 mg/kg, intraperitoneally) N-Butyl-bromide hyoscine (1 mg/kg, intraperitoneally) Flumazenil (2 mg/kg, intraperitoneally)	Strychnine (0.5 mg/kg, intraperitoneally) Pilocarpine (300 mg/kg, intraperitoneally) Isoniazid (300 mg/kg, orally) Picrotoxin (3 mg/kg, intraperitoneally)	It interacts with receptors or channels when it inhibits the action of strychnine-sensitive glycine receptors, boosts post-synaptic excitability in brain and spinal cord, for shortens of frequency and duration of strychnine-induced convulsions.	Obese et al. (2021)
42.	*Macuna pruriens* (Seeds)	(200, 300 mg/kg, orally, orally)	Petroleum ether extract	Diazepam (1 mg/kg intraperitoneally)	Pentylenetetrazole (60 mg/kg, subcutaneous) Isoniazid (iso-nicotinic acid hydrazide) (300 mg/kg, subcutaneous)	According to this study, plant extracts include compounds that help GABAergic transmission. This shows that the anxiolytic and anticonvulsant effect involve GABA receptors.	Rupali and Azharuddin (2021)

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Table 3 continued

43.	*Kochia scoparia* (Leaves)	(75, 150, 300 mg/kg, orally)	Volatile oil is isolated by hydro distilla-tion method	Diazepam (2 mg/kg, intraperitoneally) Phenobarbitone (30 mg/kg, intraperitoneally)	MES – Electric current of 50 amp (100 Hz) for 0.2 sec through corneal electrode Pentylenetetrazole (80 mg/kg, orally) Strychnine (2 mg/kg, orally)	K. scoparia may block voltage-gated sodium channels to cause its anticonvulsant effects.	Imade et al. (2021)
44.	*Anchusa italica* (Flowers)	(50, 100, 200 mg/kg, orally)	Ethanol extract	Phenobarbital (4 mg/kg, intraperitoneally)	Pentylenetetrazole (10 mg/kg, intraperitoneally)	According to reports, increased nitric oxide synthesis caused mitochondrial malfunction in neuronal cells, which then resulted in oxidative stress and ultimately increased seizure frequency. In this investigation, the PTZ groups had higher nitrite levels in their serum and prefrontal brain samples. The serum and prefrontal brain samples nitrite levels were significantly reduced by A. italica extract.	Rahimi-Madiseh et al. (2021)
45.	*Harungana madagascariensis* (Seeds)	(100, 500, 1000 mg/kg b wt. of extract, orally)	Methanol extract of H madagas-cariensis AHM 1 (n-dotriacontane) AHM 2 – (Friedelan-3-one)	Diazepam (0.5 mg/kg, intraperitoneally) Isoniazid (300 mg/kg, intraperitoneally)	Pentylenetetrazole (70 mg/kg, intraperitoneally) Picrotoxin (7.5 mg/kg, intraperitoneally)	It acts by inhibiting GABA transaminase and enhancing brains GABA receptors.	Jordan et al. (2020)

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Table 3 continued

46.	*Colebrookea oppositifolia* (Roots)	(25, 50, 100, 200 mg/kg, orally)	Acetoside isolate methanolic extract of C. opposibifolia	Flumazenil (3 mg/kg, intraperitoneally)	MES – Electric current of 60 mA for 0.2 sec through corneal electrode. Pentylenetetrazole (70 mg/kg, intraperitoneally)	It inhibits action on Gama amino butyric acid on neuronal transmission	Viswanatha et al. (2020)
47.	*Epilobium hirsutum* (Leaves)	(200 mg/kg, intraperitoneally)	Ethanol extract	Sodium valproate (100 mg/kg, intraperitoneally)	Pentylenetetrazole (65 mg/kg, intraperitoneally)	It acts by inhibit release of Glutamate excitatory neurotransmitter	Dzhafar et al. (2020)
48.	*Bidens odorata* (Leaves)	(10, 200 mg/kg, orally)	Ethanol extract	Flumazenil (2 mg/kg, orally)	Pentylenetetrazole (20 mg/kg)	It acts by inhibiting T-type calcium channels to encourage GABAergic neurotransmission.	Alonso-Castro et al. (2020)
49.	*Sapindus Mukorossi* (Fruit)	(200, 400 mg/kg, orally)	Distilled water and methanolic extract	Phenytoin sodium (20 mg/kg, orally)	Pentylenetetrazole (60 mg/kg, intraperitoneally)	Gamma-amino butyric acid binding to enhances its inhibitory effects.	Anitha et al. (2015)
50.	*Adansonia digitata* (Stem bark)	(10, 100, 1000 mg/kg, intraperitoneally)	Methanol extract	Sodium valproate (200 mg/kg b wt. intraperitoneally)	Pentylenetetrazole (80 mg/kg, intraperitoneally)	The effects of GABA are enhanced by blocking Sodium channels, which also stops the production of excitatory transmitter.	Yunusa et al. (2020)

Table 4
Some reported phytochemicals of medicinal plants used in epilepsy.

S. No.	Plants	Therapeutic active marker	Dose (mg/kg in rat model/mice)	Associated pharmacological activity and or mechanism of action	References
1.	*Carissa carandas* L.	Carissone	-	GABA is an inhibitory neurotransmitter voltage-dependent Na+ channel and antagonizes other types of neurotransmitters via blocking chloride channel which connect to GABAA receptor	Hegde et al. (2009)
2.	*Pongamia pinnata* L.	Kaempferol and quercetin,	100 mg/kg, bw for each	Decrease extension phase duration. GABA exhibits anticonvulsant effects against seizures induced via MES	Manigauha (2009)
3.	*Punica granatum* L.	Punicalagin-β and punicalagin-α,	100 mg/kg, bw	Increased antioxidant capacity, reduced GABA or lipid peroxidation (LPO) neuronal injury triggered by a neurotransmission act as presynaptic and postsynaptic position. Spinal cord glycine receptor inhibition blocked via selective competitive antagonist during Ca2+ influx through NMDA receptor activation	Mehrzadi et al. (2015)
4.	*Cardiospermum halicacabum* L.	Flavonoids, fixed oil, fat	NA	Na+ voltage-sensitive channel blockage, enhanced GABAA receptor-mediated inhibitory	Dhayabaran et al. (2012)
5.	*Solanum sisymbriifolium* Lam.	Solasodine	25 mg/kg	Chloride ion channel opening and enhanced GABAergic neurotransmission. Voltage-dependent Na+ channel inhibition	Chauhan et al. (2011)
6.	*Wedelia chinensis* M.	Alkaloid, flavonoid, glycoside, saponin	NA	Gamma amino butyric acid (GABA) is an antagonist that inhibits the GABAA receptor by pentylenetetrazole. Voltage-gated or Glutaminergic excitatory Inhibitory Na+ channel	Mishra et al. (2011)
7.	*Achyranthes aspera* L.	Betaine	900 μg/kg	Enhance GABAergic neurotransmission or inhibit benzodiazepine site of GABA receptor	Gawande et al. (2017); Ghoz and Freed (1985)
8.	*Lobelia nicotiana* folia R.	Lobeline	30 mg/kg	Enhance GABAergic release, blocking of transport or metabolism, directly bind or activate GABAA receptor	Tamboli et al. (2012)

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Table 4 continued

9.	*Hypericum scabrum* L	Essential oil, fatty acid	NA	To enhance chloride ion resistance into the brain cells while GABA activate GABAA receptor, block GABAA receptor-linked chloride ion channel that frequently open	Ebrahimzadeh et al. (2013)
10.	*Syzygium aromaticum* L.	Oleanolic acid	100 mg/kg	GABAA receptor influenced directly via inhibiting neurotransmission, non-competitive antagonists block GABAA receptors, chloride ion channel and selective competitive GABA A receptor antagonist	Lina et al. (2023); Türel et al. (2023)
11.	*Ipomoea asarifolia* (Desr)	Cardiac glycoside, saponin, steroids	NA	Neurotransmitter inhibit chloride ion influx triggered via GABAA receptor. Alpha and beta peptide subunit involve GABA receptor (picrotoxin) site. Enhance GABAergic receptor in the dentate gyrus or brain part	Chiroma et al. (2022)
12.	*Lactuca serriola* L.	Lactucin, lactucone, lactucic acid, lactucopicrin	NA	Chloride ion channel activate via GABA to enhance GABA response.	Ullah et al. (2022)
13.	*Decalepis nervosa* Wight & Arn.	Gallic acid	30 mg/kg	Decrease GABAA synapse block GABA pathway act as a GABAA receptor antagonist. NMDA and non-NMDA receptor are activated through glutamate excitatory neurotransmitter. Ion channel of Na+, K+, Ca++, and Cl- either stimulate or inhibit neuron	Das et al. (2022); Jafaripour et al. (2022)
14.	*Valeriana edulis* L.	Valepotriate	20 mg/kg	GABA are synaptic receptor in brain cortices is triggered, inhibited, or enhance GABAergic transmission	González-Trujano et al. (2021); Wu et al. (2017)
15.	*Lantana camara* L	Coniine	20 mg/kg in mice	Inhibiting GABA transaminase or increase the frequently open GABA chloride channel	Bora and Singh (2019b); Hotti and Rischer (2017)
16.	*Morinda lucida* B.	Cardenolide	100 mg/kg	Inhibit GABA neurotransmission at GABAA receptor	Estella et al. (2020); Nakhaee et al. (2021)
17.	*Morus nigra* L.	Linoleic acid	100 nmol/kg	GABA release increased or reduce brain cell damage	Ekici et al. (2014); Zehra et al. (2021)
18.	*Sapindus mukorossi* G.	Betulinic Acid	3 mg/kg single dose	GABA receptor bind and neurotransmitter activation	Anitha et al. (2015); Pozo et al. (2022)

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Table 4 continued

19.	*Adansonia digitata* L.	Epigallocatechin-3-gallate	35 mg/kg	Increased level of GABA may either directly bind or activate GABAA receptor, direct effect on GABA release, transport, and metabolism. Seizure induction and onset are tightly correlated with GABA-mediated chloride channel open. Non-competitive antagonist enhances excitatory neuron release NTs or inhibit GABA-mediated Cl influx	Xie et al. (2012); Yunusa et al. (2020)
20.	*Fumaria schleicheri* Soy Will.	Polyphenol, phenolic acid, lipophilic compound	NA	Inhibiting Ca2+ influx, GABA-barbiturate-benzodiazepine receptor complex binding site decrease glutamate excitotoxicity or decrease interleukin-1 pathway and ionotropic glutamate receptor	Prokopenko et al. (2016)

This suggests that *Viola* extracts might offer a natural alternative for managing sleep disorders and protecting the brain from the harmful effects of prolonged sleep deprivation (Dhiman et al., 2023). *Punica granatum* L. (Seed), also known as pomegranate, is noted for its positive impact on cognitive functions, particularly in the elderly. The seed extract significantly enhances general cognitive capacities and memory. Additionally, it contains Huperzine-A polyphenol, which interacts with Alzheimer's disease (AD)-related pathophysiology, helping to reduce clinical symptoms and mitigate memory loss in elderly individuals suffering from neurological diseases. This points to the potential of pomegranate seeds as a therapeutic intervention for age-related cognitive decline and neurodegenerative diseases like Alzheimer's (Mehdi et al., 2022).

Ginkgo biloba (Leaf) is widely recognized for its benefits in improving mental health and cognitive processes. The clinical assessments show that Ginkgo biloba significantly enhances patients' self-reported mental health, neuropsychological functions, memory, and overall cognitive processes. This aligns with Ginkgo's long history of use in traditional medicine for boosting cognitive function and treating disorders like dementia (Zuo et al., 2017). *Valeriana edulis* (Roots) is highlighted for its effects on sleep. A single dose of 450 mg/kg was found to reduce the number of awakening episodes, according to Shinjyo et al. This indicates that Valeriana edulis may be an effective natural remedy for improving sleep quality, particularly in individuals who suffer from frequent awakenings during the night (Shinjyo et al., 2020). Hence, provides evidence that plant extracts from *Viola tricolor*, *Punica granatum*, *Ginkgo biloba*, *Valeriana edulis*, etc., possess significant neuroprotective and cognitive-enhancing properties. These plants could potentially be used as natural alternatives or complementary therapies for managing neurodegenerative diseases, cognitive decline, and sleep disorders. The clinical assessments underscore the importance of further research to fully understand the mechanisms behind these benefits and to optimize their use in medical practice.

5. BIOMOLECULAR APPROACHES TO INVESTIGATION AND AMELIORATION OF EPILEPSY DISORDER

Epilepsy's pathophysiology involves abnormal neural activity due to an imbalance between excitatory and inhibitory neurotransmission in the brain. This imbalance often results from dysregulated ion channels, neurotransmitter receptors, and synaptic proteins, leading to excessive electrical discharges. These disruptions create hyperexcitable neuronal networks, which can trigger and propagate seizures. Additionally, structural abnormalities, genetic mutations, and inflammation can contribute to epileptogenesis. Understanding these mechanisms helps in developing antiepileptic therapies that target specific pathways, such as enhancing inhibitory GABAergic transmission, reducing excitatory glutamatergic activity, and stabilizing neuronal membranes, ultimately preventing seizure occurrence and progression.

Mechanistic insights into the pathophysiological aspects of epilepsy reveals modulation of neural excitability, synaptic transmission, and neuronal network stability. This imbalance can be attributed to the dysregulation of ion channels, neurotransmitter receptors, and synaptic proteins. However, antiepileptic drugs (AEDs) that enhance GABAergic (inhibitory) neurotransmission or inhibit glutamatergic (excitatory) transmission directly target this imbalance, reducing the likelihood of seizure initiation and propagation. Sodium and calcium channel blockers, which stabilize neuronal membranes and prevent repetitive firing, also play a crucial role in managing epilepsy by reducing hyperexcitability. Additionally, AEDs that modulate synaptic plasticity and network connectivity help in normalizing aberrant neural circuits, thereby restoring balance and preventing seizures (Brancati et al., 2023; Kim et al., 2021; Tokariev et al., 2022). The neuroprotective effects of certain AEDs also contribute to their efficacy by preventing the neuronal damage associated with prolonged seizures (status epilepticus). By addressing these underlying pathophysiological mechanisms, AEDs provide a clear rationale for their antiepileptic effects, offering therapeutic benefits in managing and controlling seizures in individuals with epilepsy.

According to the recent revealed studies, the pathophysiology of epilepsy involves mitochondrial malfunction, blood-brain barrier (BBB) dysfunction and growth of microglia and astrocytes, causing reactive oxygen species (ROS) to develop. The most widely recognized theory about the pathophysiology of epilepsy is undoubtedly one that involves impaired GABA functions in brain. It has been shown through experimental modelling and clinical neuroimaging of patients that seizures can cause neuronal apoptosis. Pathways for apoptosis role in aetiology of numerous epilepsy forms, including temporal lobe epilepsy (TLE) (Auxéméry et al., 2011; Gupta et al., 2014; Imade et al., 2021). Patient's life is significantly impacted by both treatment-related difficulties and the unpredictable occurrence of epileptic seizures. Additionally, the antiepileptic medications (AED) on the market place are not very effective at stopping epileptogenesis. Therefore, there is a need for novel therapies that are effective at controlling seizures in epileptic patients. The preconditioning method has the potential to be used as an alternative therapeutic strategy because it has shown to be effective in suppressing epileptogenesis. Establishing novel neuroprotective strategies against seizure damage and epileptogenesis therefore requires a thorough knowledge of molecular mechanisms via brain tolerance conferred on preconditioning (Blank et al., 2021; Shao et al., 2019; Wong & Guo, 2013). In this review, we summarize the research that has been done so far on the pathophysiology of epilepsy and discuss current approaches for treat epilepsy. We will emphasize the promising potential of novel therapeutic targets like the preconditioning process. We will also emphasize how gene remodeling and the biogenesis of mitochondria contributes to the neuroprotective effects of preconditioning. The mechanism of action of Antiepileptic Plant based Secondary metabolites has been depicted in Figure 4.

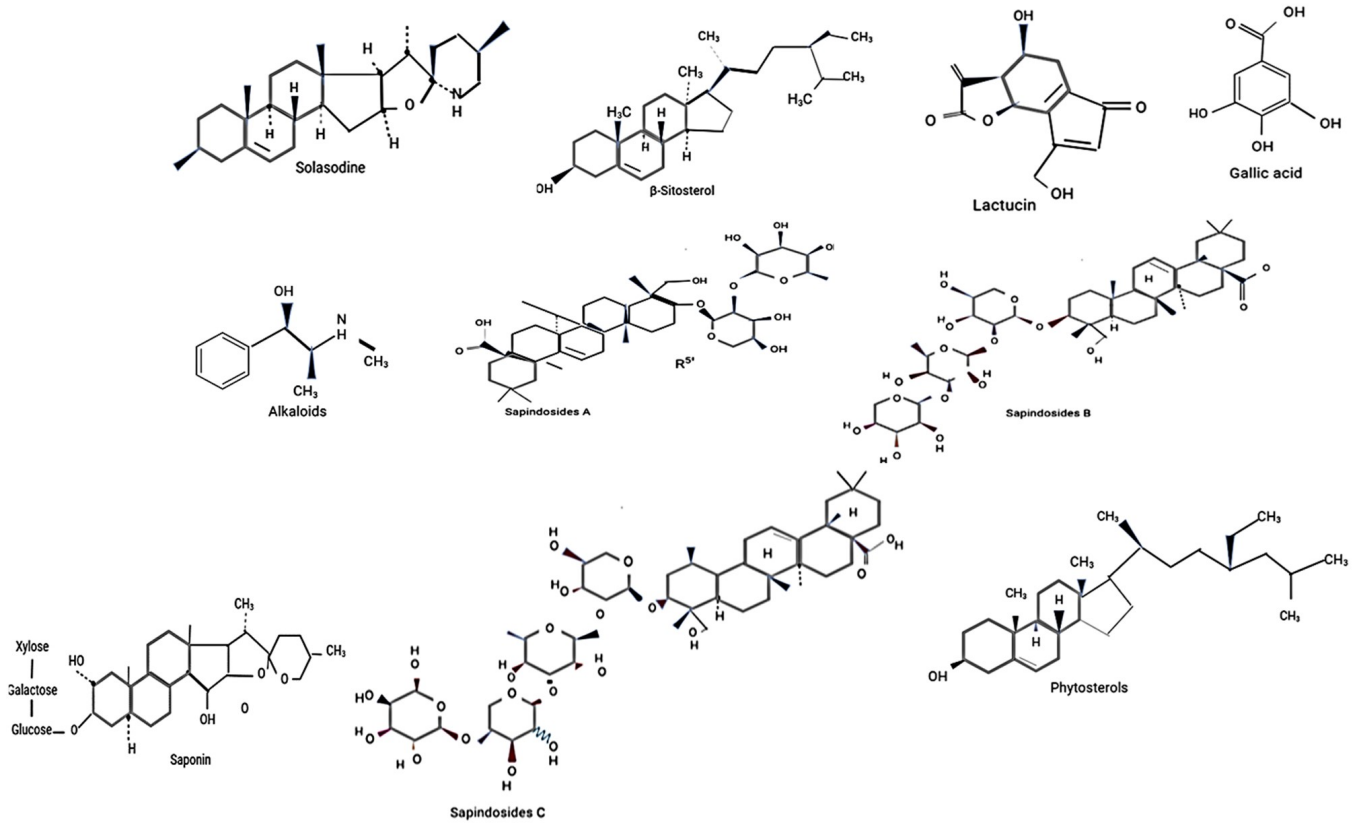

Figure 2. Reported phytochemicals for anti-epileptic activity (1-10).

6. CHALLENGES AND FUTURE PERSPECTIVES AMONG POLYHERBAL FORMULATIONS

Herbal medicine has been a cornerstone of healthcare across cultures for thousands of years, serving as a primary means of treating a wide array of acute and chronic ailments. In both advanced and developing countries, herbal medicines and their formulations have been extensively utilized, blending the medical expertise of traditional practitioners with time-tested remedies. Despite the rapid advancements in modern medicine, the demand for herbal treatments continues to grow, driven by their perceived effectiveness, safety, and minimal adverse effects. In countries like India, the integration of traditional medical knowledge into everyday healthcare practices is particularly pronounced. India's rich heritage in traditional medicine is well documented and widely practiced through systems such as Ayurveda, Siddha, and Unani. These systems rely heavily on herbal and herbal-mineral compositions, creating a vast market for herbal products that are increasingly sought after for their therapeutic and nutritional benefits (Ekbbal et al., 2023; Gaurav et al., 2022, 2023).

Globally, the appeal of herbal products is on the rise. Consumers are drawn to these natural remedies, often regarded as safer alternatives to synthetic drugs. The preparation and commercialization of herbal extracts or purified bioactive components have taken various forms, catering to the diverse needs of the global market. Products that incorporate more than two herbal extracts, known as polyherbal products, are particularly popular due to their complementary and potentiating effects. These products are believed to offer prophylactic or therapeutic benefits that surpass those of single-herb formulations. However, while the popularity of herbal products is undeniable, there is a critical need for more rigorous scientific research to validate their efficacy and safety. Despite their widespread use, many herbal products have not undergone extensive research to confirm their effectiveness. This lack of research can put patients or consumers at risk of adverse reactions, potentially leading to acute or chronic toxicity (Ahmad et al., 2021; Ali et al., 2023; Zahiruddin et al., 2020).

One significant area of concern is the neurotoxicity associated with some polyherbal preparations. These formulations can sometimes contain heavy metals such as lead, mercury, and arsenic, which are known to cause severe neurotoxic effects. While general toxicity testing is often performed on herbal products, specific neurotoxicity assessments are frequently overlooked. This oversight highlights the need for more comprehensive safety evaluations of herbal formulations, particularly polyherbal products. The primary drawback of using polyherbal formulations for preventive or therapeutic purposes lies in the lack of reliable scientific data on several critical aspects. These include the full metabolite profile,

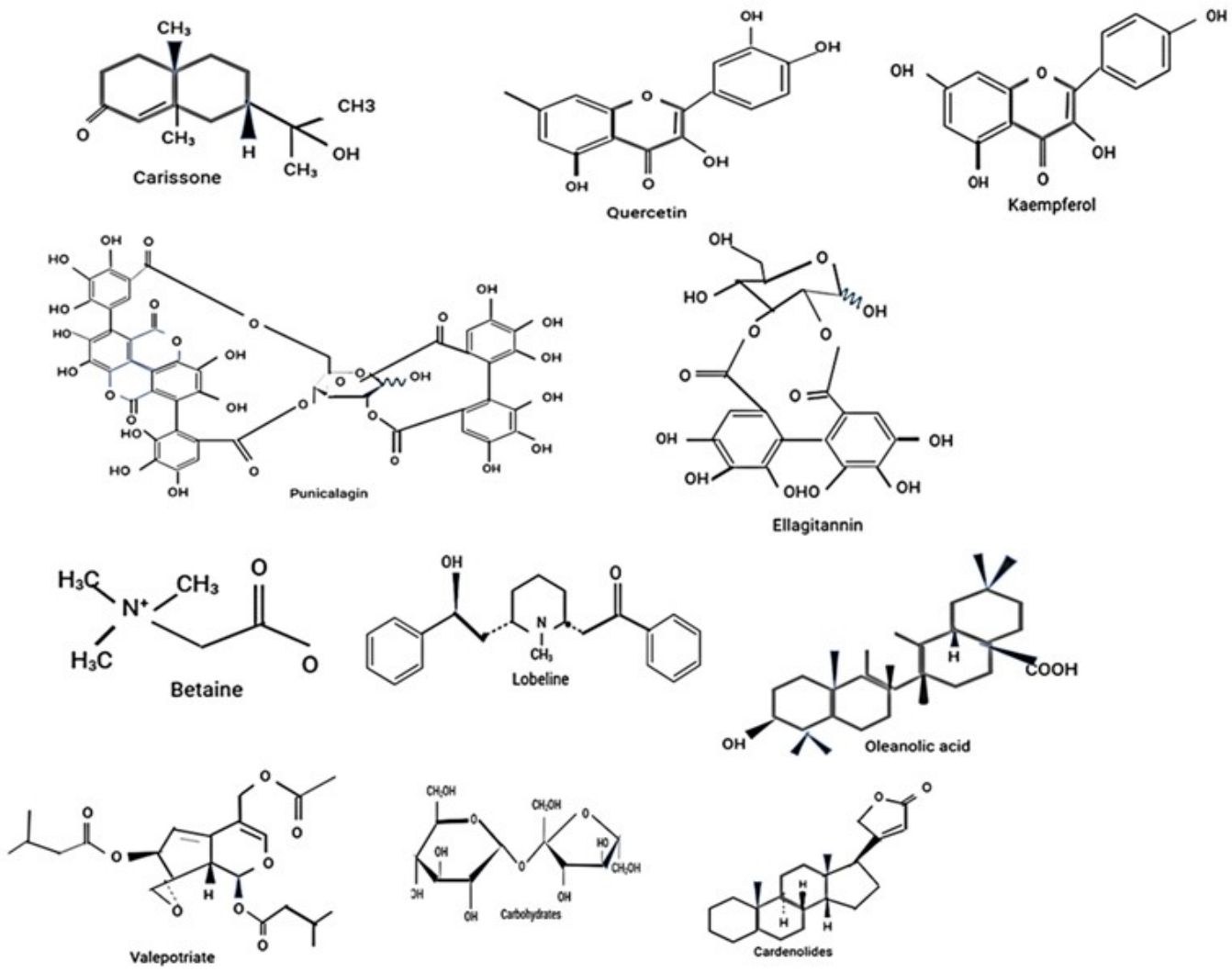

Figure 3. Reported phytochemicals for anti-epileptic activity (11-21).

human equivalent dose, potential side effects, and available antidotes. Without this information, the safety and efficacy of polyherbal formulations remain uncertain, limiting their potential as reliable treatment options (A. Gaurav et al., 2023; Z. Gaurav et al., 2020).

India, with its deep-rooted tradition in herbal medicine, holds significant potential to become a global leader in the production and commercialization of both single and polyherbal formulations (PHFs). A SWOT (Strengths, Weaknesses, Opportunities, and Threats) analysis reveals that India's strengths in this field are considerable. The country possesses a wealth of botanical resources, a strong tradition of herbal medicine, and a growing market for natural health products. However, to fully capitalize on these strengths, there is a need for substantial investment in research and development. The opportunities for growth in the polyherbal formulations market are substantial. As global interest in natural and alternative therapies continues to rise, the demand for these products is expected to expand in both developed and developing nations. However, the challenges associated with developing and commercializing polyherbal formulations should not be underestimated. The lack of standardized extracts, variability in the quality of raw materials, and the absence of detailed pharmacokinetic studies are significant hurdles that need to be addressed (Ekbbal et al., 2022; Tadesse et al., 2023).

Future research in this area must focus on several key areas to overcome these challenges. Detailed pharmacokinetic studies are essential to understand how these herbal formulations are absorbed, distributed, metabolized, and excreted in the body. Such studies will provide valuable insights into the appropriate dosages and potential interactions between different herbal components within polyherbal formulations. Advancement in the modern analytical tools such as chromatographic and spectroscopic techniques lay down a new insight to unravel the mystery behind pharmacodynamic and kinetic behavior of drugs or medicinal plants. the Additionally, large-scale

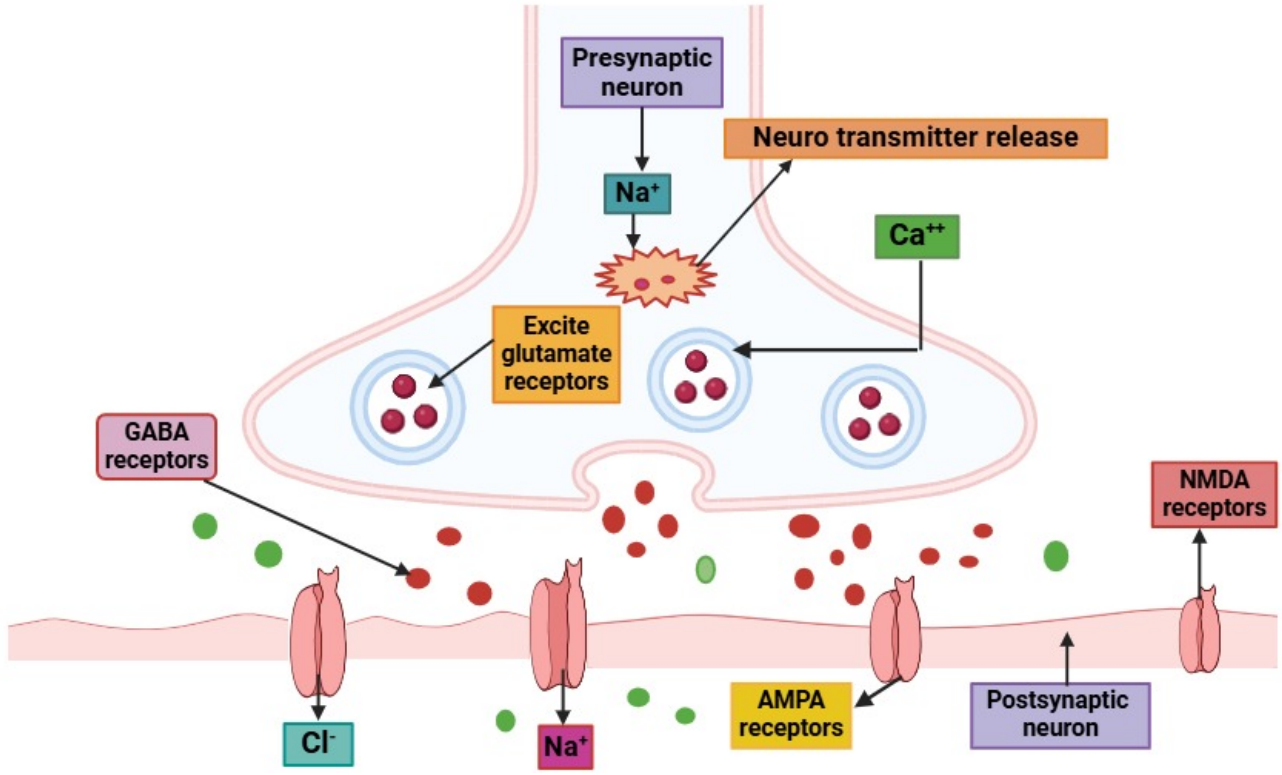

Figure 4. Mechanism of Action of Anti-Epileptic Plant-Based Secondary Metabolites. Based on review findings, various plant metabolites exhibit anti-epileptic properties through different mechanisms. Valepotriates and isovalerate act on GABA synaptic receptors in brain cortices, triggering, inhibiting, or enhancing GABAergic transmission. Alkaloids, tannins, carbohydrates, flavonoids, terpenoids, glycosides, and phenols inhibit GABA transaminase or increase the frequency of open GABA chloride channels. Cardenolides, alkaloids, and saponins inhibit GABA neurotransmission at the GABAA receptor. Flavonoids, anthocyanins, and phenolics increase GABA release or reduce brain cell damage. Sapindosides A, B, C, and D, along with mukorozi saponins (E1 and Y1), bind to GABA receptors, activate neurotransmitter activity, inhibit voltage-dependent Na+ channels, and regulate voltage-gated or glutamatergic excitatory Na+ channels. These diverse mechanisms highlight the potential of plant-based secondary metabolites in epilepsy management. Moreover, the components like punicalagin increase antioxidant capacity, reduced GABA or lipid peroxidation (LPO) neuronal injury triggered by a neurotransmission act as presynaptic and postsynaptic position. Spinal cord glycine receptor inhibition blocked via selective competitive antagonist during Ca2+ influx through NMDA receptor activation.

clinical trials are necessary to establish the safety and efficacy of these products in diverse populations. These trials will help to build a robust evidence base that can guide the use of polyherbal formulations in clinical practice. The development of standardized extracts is another critical area for future research. Standardization ensures that herbal products contain consistent levels of active ingredients, which is essential for achieving reliable therapeutic outcomes. Currently, the lack of standardization is a significant barrier to the widespread acceptance of polyherbal formulations in the global market. Research efforts should focus on identifying the key active compounds in these formulations and developing standardized methods for their extraction and quantification (Khan et al., 2024; Zahiruddin et al., 2016).

Moreover, the safety of polyherbal formulations must be rigorously evaluated, with a particular focus on potential neurotoxic effects. Heavy metal contamination is a well-documented risk associated with some herbal products, particularly those that include mineral components. Future research should prioritize the development of safer formulations, free from harmful contaminants, and the implementation of strict quality control measures throughout the production process. In addition to these scientific and technical challenges, the commercialization of polyherbal formulations also requires addressing regulatory issues. The global market for herbal products is highly fragmented, with varying regulations across different countries. Harmonizing these regulations and establishing clear guidelines for the approval and marketing of polyherbal formulations will be crucial for expanding their reach in the global market. Collaborative efforts between governments, regulatory agencies, and the herbal industry are needed to create a supportive environment for the growth of this sector. Healthcare professionals need to be well-informed about the benefits and risks of polyherbal formulations to make evidence-based recommendations to their patients (Z. Gaurav et al., 2020; Gautam et al., 2021; Jawal et al., 2024; Khan, Gautam, et al., 2022).

In contrast, the potential for growth in the market for herbal and polyherbal formulations is immense, but realizing this potential will require a concerted effort on multiple

fronts. Future research must focus on addressing the current gaps in scientific knowledge, particularly through detailed pharmacokinetic studies, large-scale clinical trials, and the development of standardized extracts. By investing in research and development, ensuring rigorous safety evaluations, and overcoming regulatory challenges, India has the opportunity to emerge as a global leader in the field of herbal medicine. The future of polyherbal formulations is bright, but its success will depend on our ability to navigate the complexities of science, regulation, and market dynamics.

7. CONCLUSION

The invention of an entirely novel molecule has resulted in essential studies on herbal medicinal species offer an accurate list of all traditional plants used to treat brain disorders. The investigation revealed knowledge about the physiology of brain disorders and their prevalence and incidence. The lack of knowledge about existing herbal medicinal plants via brain competencies persists as a worldwide health issue. It can be concluded that research on medicinal plants has revealed antiepileptic properties and provided insights into the complex mechanisms of epilepsy. The majority of individuals believe that phytomedicines are safe and have fewer adverse effects than synthetic medications. Since the utilization of herbal remedies as self-medicating is rising, it is important to record the use of herbal treatments when collecting an individual's clinical information. Most drugs that increase GABA levels in the brain are being found to work as anticonvulsants against MES, PTZ, strychnine, and pilocarpine-induced seizures. As an outcome, in searching to discover novel medicine, therapeutic plants utilized in the management of brain disorders might be utilized when it can be identified that these particular plants are sufficiently successful in alleviating disorders of the brain. Modern and traditional herbal therapies, which must be developed.

ABBREVIATIONS

WHO - World Health Organization
QOL - Quality of Life
EEG - Electroencephalogram
PTZ - Pentylenetetrazole
PT - Picrotoxin
MES - Maximal Electroshock
NMDA - N-methyl-D-asparate
SN - Strychnine
NH - Isoniazid
ROS - Reactive Oxygen Species
BBB - Blood Brain Barrier
GABA - Gamma Amino Butyric acid
AED - Anti-epileptic medications
TLE - Temperol lobe epilepsy
PHF - Polyherbal Formulations

CONFLICTS OF INTEREST

Authors declare no conflict of interest.

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AUTHOR CONTRIBUTIONS

Gaurav - Research concept and design, Pooja Sinoriya - Collection of data, Pooja Sinoriya - Writing the article, Gaurav - Critical revision of the article, Gaurav - Final approval of the article.

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