CHAPTER N0.

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Drug Therapy and Natural Remedies: A Holistic View of Epilepsy Management

HOORIA GUL[1,2], RABIA ALTAF[1], HUMAIRA MAJEED KHAN[3], AHSAN SHABBIR [2,4], FARIA QAISER[5], DOUA ILYAS[5,6], ASRA IFTIKHAR[7], AMNA KHAN ADIL[7]

[1]School of Pharmacy, University of Management and Technology, Lahore, Pakistan
[2]Mirpur University of Science and Technology, Mirpur, Azad Jammu and Kashmir, Pakistan
[3]Faculty of Pharmaceutical and Allied Health Sciences, Lahore College for Women University, Lahore, Pakistan
[4]Ulster University of Birmingham, Birmingham, United Kingdom
[5]Department of Pharmacy, Quaid-i-Azam University, Islamabad, Pakistan
[6]Riphah Institute of Pharmaceutical Sciences, Riphah International University, Islamabad, Pakistan
[7]Akhtar Saeed College of Pharmacy, Rawalpindi, Pakistan
*Correspondence: asraiftakhar@yahoo.co.uk

ABSTRACT: Epilepsy is a common brain disease and millions of people around the world suffer from it. In 2016, approximately 45.9 million individuals globally were living with active epilepsy, with a prevalence of 62.15 per 100,000 people. Seizures are currently classified on a broader level as focal, generalized, and unknown onset, and on a further level as motor and non-motor. According to the classification system of the International League Against Epilepsy (ILAE), these etiologies can be broadly categorized into six groups: structural abnormality, genetic predispositions, infectious agents, metabolic dysfunctions, immune-mediated response, and neurodegenerative processes. Mutations in genes coding for synaptic components, e.g. Germany synapses, have been linked to epilepsy, which can be caused by such an imbalance in it. TRPV1 is overexpressed in regions in brain linked to epilepsy: the hippocampus, amygdala, and cortex. The channel is involved in seizure susceptibility and propagation, which may result from its effects on neuronal excitability and inflammation. The antiepileptic properties of *Acacia nilotica* are mainly associated with the bioactive compounds, flavonoids, saponins and tannins. These compounds are believed to have neuroprotective properties by acting on the release of neurotransmitters and by decreasing oxidative stress, which are fundamental factors in the onset and the development of epileptic seizures.
Keywords: Epilepsy, metabolic dysfunctions, antiepileptic, neuroprotective

INTRODUCTION

In high-income countries, the rate of epilepsy stays consistent across the world, between 40 and 70 cases of epilepsy per 100,000 people per year. Among older people (aged >50 years), the incidence increases with age, with a peak incidence in people over 70 years (Thijs et al., 2019). The World Health Organization (WHO) has recognized epilepsy as an important public health issue because of the high prevalence of the condition among all age groups and geographic regions, the high burden of the disease on disability adjusted years of life (DALYs), the effects on psychosocial well-being, and the stigma of epilepsy in society. A major step was taken in November 2020. WHO member states adopted a unanimous resolution. They worked with the World Federation of Neurology and the European Federation of Neurological Associations. They committed to developing and implementing the Intersectoral Global Action Plan on Epilepsy and Other Neurological Disorders. This plan aims to improve care and support for people with epilepsy (Guekht et al., 2021). Epilepsy can also cause mental health complications. It may increase the risk of early death (Klein et al.2024). This stigma leads to exclusion and discrimination. It affects key areas such as employment, education, and social interactions. It ultimately diminishes their quality of life (Octaviana et al., 2025).

CLASSIFICATION OF SEIZURE

The International League Against Epilepsy (ILAE) has created an updated operational classification of seizure types (Table 1), which is directed to clinical rather than mechanistic issues. The revision covers better clarity in nomenclature, ease of categorization of seizures as focal or generalized, and classification in case of indeterminate onset. Seizures are currently classified on a broader level as focal, generalized and unknown onset and on a further level as motor and non-motor characterized. For focal seizures, awareness is also considered retained or impaired (Fisher et al., 2017).

PREVALENCE OF EPILEPSY

Epilepsy is a common brain disease and millions of people around the world suffer from it. In 2016, approximately 45.9 million individuals globally were living with active epilepsy, with a prevalence of 62.15 for 100,000 people (Beghi et al., 2019). There is a range for prevalence rates based on regional and demographic factors. A 2017 meta-analysis showed a point prevalence of active epilepsy to be 6.38 per thousand people, with a lifetime prevalence of 7.60 per thousand people. It is important to note that lifetime prevalence was higher in low and middle-income countries (8.75 per 1,000) compared

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Table 1. Classification of seizure (Falco-Walter et al., 2018)

Type of Seizure	Description	Subtypes	Characteristics
Focal Seizures	Seizures starting in one area of the brain (formerly "partial seizures")	Aware (formerly simple) Impaired awareness (formerly complex)	Can spread to other areas Can be motor or non-motor
Generalized Seizures	Seizures that start in both hemispheres of the brain at once.	Motor: tonic-clonic, myoclonic, atonic, etc. Non-motor: absence seizures	Awareness is typically impaired
Unknown Onset Seizures	When the starting point of the seizure is not known	Motor: tonic-clonic, other motor Non-motor	Can be reclassified if more information becomes available
Unclassified Seizures	Seizures that cannot be clearly classified into the above categories.	Not Available	Used when insufficient information is available

to high-income countries (5.18 per 1,000). In Pakistan, a study from Sheringal, Khyber Pakhtunkhwa reported the prevalence of epilepsy is at 9.98 per 1,000 persons among persons of all age groups, with 74% of cases occurring in persons under 18 years of age (Akhter et al., 2018). Between 1990 and 2016, its global age-standardized prevalence of idiopathic epilepsy was relatively stable with a non-significant change of 6.0%; however, 24.5% decrease in age standardized mortality rates, and disability adjusted life years (n= 19.4%), were recorded in the same period, indicating improvements in epilepsy management and care (Beghi et al., 2019).

ETIOLOGY OF EPILEPSY

The cause of the seizure is important for assessing the risk of its recurrence, and thus the diagnosis of epilepsy. According to the classification system of the International League Against Epilepsy (ILAE), these etiologies can be broadly categorized into six groups: structural abnormality, genetic predispositions, infectious agents, metabolic dysfunctions, immune-mediated response, and neurodegenerative processes. Notably, neurodegenerative causes are frequently addressed as separate categories in view of their emerging importance in contemporary research and clinical management of epilepsy (Balestrini et al., 2021).

PATHOPHYSIOLOGY AND MECHANISM OF DEVELOPMENT OF SEIZURE

A key variable in the initiation of the seizure is disrupting the balance of both excitatory and inhibitory signals in the brain. This imbalance can be caused by a reduction in inhibitory neurotransmission (e.g., reduced activity of neurotransmitter systems like one of the neurotransmitters "Gamma Amino Butyric Acid") or by an increase in excitatory neurotransmitters (e.g., increased activity of neurotransmitters like the neurotransmitter "Salicin"). Mutations in genes coding for synaptic components, e.g. Germany synapses, have been linked to epilepsy, which can be caused by such an imbalance. Seizures are a result of an imbalance between the excitatory and inhibitory processes in the brain, resulting in excessive and synchronized electrical discharges of brain cells. This hyper excitability can be caused by a variety of factors, some of which are genetic mutations, structural abnormalities, metabolic disturbances, infections, and inflammatory processes. (Koh et al., 2021).

Epileptic seizures are the result of abnormal and synchronous neuronal activity caused by different pathophysiological mechanisms. One important factor is brain excitation and inhibition imbalances; excessive excitation or reduced inhibition can result in neuronal hyper-excitability and synchronization. Inflammatory processes are also significant in this, pro inflammatory cytokines such as interleukin-1(IL-1) and tumor necrosis factor-alpha (TNF-alpha) released by activated microglia and astrocytes, increase neuronal excitability and contribute to seizure activity. Blood brain barrier (BBB) allows immune cell infiltration of the central nervous system, which further worsens inflammation and neuron dysfunction. TRPV1, commonly referred to as the capsaicin receptor, was first discovered in 1997 and is involved in a number of physiological processes, among them temperature sensation, pain transmission, neuroinflammation, and neurotransmission. TRPV1 is overexpressed in regions in brain linked to epilepsy: the hippocampus, amygdala, and cortex. The channel is involved in seizure susceptibility and propagation, which may result from its effects on neuronal excitability and inflammation. This channel is involved in seizure susceptibility and progression, which may be mediated by its effect on neuronal excitability and inflammation (Socala et al., 2024).

INCIDENCE OF EPILEPSY

A 2025 study using data from the Global Burden of Disease (GBD)2021 was able to reveal wide differences in the burden of idiopathic epilepsy between regions, genders, and ages. The research highlighted especially high levels of incidence and mortality in low- and middle-income countries, showing the need for better epilepsy diagnosis and care in these countries (Xu et al., 2025). In Pakistan, epilepsy is a major health concern. A review of literature indicated an overall prevalence of approximately 1% in the country. Notably, a higher prevalence was reported in populations under 30 years of age, which may be attributed to factors such as genetic predisposition and prenatal complications, central nervous system infections during early life, and head injuries (Khatri et al., 2023).

CURRENT ANTIEPILEPTIC TREATMENTS

As of 2025, epilepsy management mainly consists of anti-epileptic drugs (AEDs) based on the type of seizure experienced and the profile of the patient (Table 2). For generalized onset seizures, first-line monotherapies include lamotrigine and levetigretam with valproic acid being reserved for men and women not of childbearing potential due to risk of teratogenic effects. In focal onset seizures, lamotrigine and

Table 2. Anti-epileptic drugs: their clinical applications and adverse effects (Ritter, 2020)

AED (Anti-epileptic drugs)	Clinical applications	Common Adverse Effects
Phenytoin	Partial and secondarily generalized seizures, status epilepticus	Nystagmus, ataxia, gingival hyperplasia, rash, sedation
Carbamazepine	Partial seizures, generalized tonic-clonic seizures	Hyponatremia, sedation, rash, dizziness, ataxia
Valproic Acid	Broad-spectrum, including absence seizures, Lennox-Gastaut syndrome	Weight gain, tremor, hair loss, hepatotoxicity, pancreatitis
Phenobarbital	Generalized tonic-clonic seizures, status epilepticus, and certain other seizures	Sedation, cognitive impairment, tolerance, dependence
Primidone	Partial and generalized tonic-clonic seizures	Sedation, cognitive impairment, tolerance, dependence, less effective than Phenobarbital
Gabapentin	Partial seizures, neuropathic pain	Sedation, dizziness, ataxia, somnolence
Lamotrigine	Partial seizures, generalized tonic-clonic seizures	Rash, dizziness, headache, sedation, fatigue
Topiramate	Partial seizures, generalized tonic-clonic seizures, migraine prophylaxis	Cognitive impairment, weight loss, kidney stones, metabolic acidosis
Tiagabine	Partial seizures	Somnolence, tremor, cognitive impairment, anxiety

levetiracetam are also preferred in such cases, with carbamazepine as an alternative in the unavailability of both the above drugs. Along these lines of treatment, nearly 30 percent of patients are confronted with drug-resistant epilepsy (DRE), thus prompting exploration of new treatment objectives, including lactate dehydrogenase inhibitors and glycogen synthetase kinase 3 beta inhibitors. In addition, there are non-pharmacological interventions that can be considered for the management of DRE, such as surgery, ketogenic diets, and neurostimulation techniques (Belete, 2023).

Conventional antiepileptic drugs (AEDs) play vital roles in the treatment of epilepsy, but holistic limitations arise in the approach. Of particular concern is drug-resistant epilepsy, which affects about 30% of patients, in which the seizures are not controlled despite trials of at least 2 appropriately chosen, dosed AEDs (Kwan et al., 2010). Additionally, many AEDs are associated with having adverse effects such as central nervous system symptoms, dizziness, fatigue, cognitive disturbances, etc., effects that can impact the patient's quality of life (Ventola, 2014). Some adverse effects, such as sodium valproate, have special risks, e.g., use during pregnancy is associated with increased incidence of birth defects and developmental disorders. In addition to that, some medications may paradoxically increase seizures, which further illustrates the complexity of epilepsy management (Shariff et al., 2024).

ROLE OF MEDICINAL PLANTS IN EPILEPSY MANAGEMENT

In addition to the alkaloids, other phytochemicals, consisting of flavonoids, terpenoids and saponins, have been identified with potential anti-epilepsy action. These compounds may have their effects by antioxidant action, anti-inflammatory action and by modulating synaptic functions. For instance, flavonoids have been found to influence the transmission of neurotransmitters known as gamma-aminobutyric acid, which contributes to their anticonvulsant effect (He et al., 2024). Ethnopharmacological studies have documented the use of various medicinal plants in the treatment of epilepsy across different cultures. A comprehensive review highlighted 114 plants traditionally used in the treatment of epilepsy: 15 of them are subjected to experimental validation of their anticonvulsant properties. These studies frequently include the investigation of the effect of plant extracts in animal models to understand its respective potential of action (Kalra et al., 2024). Medicinal plants provide a valuable reservoir of bioactive compounds with potential anticonvulsant effects. Ongoing research into these natural products will potentially lead to the development of novel, effective, and available treatments for epilepsy, especially for patients who are resistant to the available pharmacological treatment options (Waris et al., 2024).

IMPORTANCE OF PHYTOTHERAPY IN SEIZURE MANAGEMENT

Phytotherapy - the use of plant-based treatments - in seizure management has been discovered as a promising strategy, as well as for treating patients who are unresponsive to traditional anti-seizure drugs. Recent investigations have discovered a variety of medicinal plants and their active constituents with anticonvulsant properties, including mechanisms such as modulation of the neurotransmitter system, antioxidant activity and anti-inflammatory properties. In 2023, a review on the efficacy and safety of the use of Chinese herbal medicine as an adjunctive therapy in post stroke epilepsy showed that seizures were controlled better and that there were fewer adverse effects. Additionally, a review published in 2024 described the pharmacological targets and mechanisms of action of different types of phytochemicals, underlining the potential of these compounds for developing new therapies against epilepsy. Not to mention the incorporation of therapeutic modalities in epilepsy therapy regimen may provide effective and well-tolerated alternatives in seizure management (Sun et al., 2023).

TRADITIONAL USE OF ACACIA NILOTICA IN NEUROLOGICAL DISORDERS

Acacia nilotica, the traditional name of which is Kakkar, has been used traditionally by various systems of traditional medicine like Unani, Traditional Chinese medicine, Ayurveda, etc., for neurological disorders, inflammation, and diabetes. Recent scientific explorations have been done to advance its neuroprotective properties (Alharbi and Azmat, 2015; Rauf et al., 2024). *Acacia nilotica* may be a shrub in poor growing conditions. It has a short, thick cylindrical trunk (about 1 meter in diameter), covered with grey bark, and its crown is either flattened or rounded. The root system differs depending on

environmental conditions and subspecies, having a deep taproot in arid zones and extensive lateral roots in flooded zones. Its leaves are alternate and compound, and 5 - 15cm long, with 7 - 36 pairs of small, elliptical, grey-green, hairy leaflets. The flowers are fragrant and in shades of bright yellow. The tree bears linear, flattened, narrow pods (without shattering), 4 to 22 cm in length, 1 to 2 cm in width, with dark brown to grey color and smooth or velvety texture. Each pod holds 8 to 15 blackish and flattened elliptical seeds. The bark of *Acacia nilotica* is rich in tannins (12-20%), terpenoids and saponins, the total extract of which is especially rich in phenols. The root contains octacosanol and botulinum, among others (Foyzun et al., 2022). In research conducted in Nigeria in collaboration with the National Center of Scientific Research of France, Ahmadu et al. have been able to extract, purify, and identify two novel compounds, ethyl gallate and (+)-catechin, from the bark of bacteria bark, respectively (Manzo et al., 2019).

The common names include Babul, Prickly acacia, Black piquant, Egyptian acacia, Indian gum Arabic tree, Gum Arabic tree, Thorn mimosa, Thorny acacia, Kikar, Sant tree. *Acacia nilotica* is classified under Domain Eukaryota, Kingdom Plantae, Phylum Spermatophyta, Subphylum Angiospermae, Class Dicotyledoneae, Order Fabale, Family Fabaceae, Subfamily Mimosoideae, Genus Acacia and Species *Acacia nilotica*. The genus *Acacia nilotica*, with more than 1,350 species, is composed mostly of medium-sized trees, usually growing to a height of between 15 and 18 meters, and woods ranging in diameter from 2 to 3 meters. These trees have a wide, low, spreading, and almost symmetrical crown. The bark is dark brown to black, deeply fissured with conspicuous vertical grooves exposing (Bargali and Bargali, 2009).

ANTI-EPILEPTIC PLANT EXTRACTS

Medicinal plants have shown potential for the treatment of refractory epilepsy with seizure and cognitive impairment. Traditional herbal remedies still offer a rich potential source of the development of antiepileptic drugs, proclaiming the effects of these drugs to be therapeutically important. However, further studies need to be conducted to investigate metabolic pathways, toxicity, clinical trials and structural optimization to further their application in modern medicine (Ohanme et al., 2024).

Medicinal plant extracts are getting increasingly noticed as potential alternatives in the treatment of epilepsy and have the potential to be better than conventional therapy due to fewer side effects, cultural acceptability, and cost-effectiveness. Recent studies have established the presence of several phytochemicals that possess anticonvulsant properties and thereby support traditional claims about their use and open the door for the development of new therapeutic agents. Almost 60 natural products from 80 plant species are common for traditional medicine for epilepsy in Africa and Asia. These compounds are: alkaloids, flavonoids, saponins, and terpenoids, and they manifest mechanisms such as modulating the system like the neurotransmitters in the nervous system (GABA and glutamatergic system), antioxidant effects, and neuroprotection (He et al., 2024).

Some flavonoids, such as apigenin and rutin, have shown articulate anticonvulsant activity in animals. Apigenin (Ajuga integrifolia, Olea europaea) acts on the gamma aminobutyric acid (GABA) - A receptor and inhibits glutamatergic neurotransmission and has antioxidant protection (Birhan, 2022). Molecular docking analysis has shown the potential of phytochemicals such as quercetin, curcumin, resveratrol and berberine as antiepileptic agents based on their binding affinities with neurological targets (Raut and Mishra, 2024).

The antiepileptic properties of *Acacia nilotica* are mainly associated with the bioactive compounds, flavonoids, saponins and tannins. These compounds are believed to have neuroprotective properties by acting on the release of neurotransmitters and by decreasing oxidative stress, which are fundamental factors in the onset and the development of epileptic seizures. Flavonoids in *Acacia nilotica,* including quercetin, are known to possess antioxidant and also anti-inflammatory features which can donate in addressing the oxidative stress associated with epileptic activity in a pupil brain. Tannins contribute to the neuroprotective effects because of their ability to decrease oxidative stress, another factor in seizure activity. The tannins in *Acacia nilotica* can protect neuronal cells against free radical damage, which aids brain health and thereby prevents epilepsy. Ethnopharmacological studies have reported the use of different medicinal plants for the management of epilepsy among different cultures. A comprehensive review listed 114 plants used for epilepsy treatment traditionally, with 15 of them in the process of experimental validation of anticonvulsant properties. These types of studies frequently include testing the action of plant extracts in animal models in order to try to understand their possible modes of action (Kalra et al., 2024). Medicinal plants represent a significant treasure of bioactive compounds having possible anticonvulsant effects. Ongoing investigation into these natural products could result in the discovery of novel, effective and accessible epilepsy treatment, specifically in patients resistant to currently available pharmacological treatment (Waris et al., 2024).

IMPORTANCE OF PHYTOTHERAPY IN SEIZURE MANAGEMENT

Phytotherapy, which is the use of plant-based remedies, has become a promising idea in the management of endocrine disorders, particularly in patients who have not responded to the treatment of conventional anti-epileptic drugs. Recent studies have encountered various medicinal plants along with their active constituents having anticonvulsant activity by various mechanisms, such as modulation of neurotransmitter systems, antioxidant activity, and anti-inflammatory activity. In 2023, a review focusing on the efficacy and safety of Chinese herbal medicine as adjuvant treatment for post stroke epilepsy revealed evident improvement of seizure control and lower levels of adverse effects. Additionally, the pharmacological targets and mechanisms that several phytochemicals exhibit were reviewed in detail during a review in 2024, which seems to portend to well for the use of new antiepileptic therapies. Integrating the application of phytotherapy into the treatment regimens of epilepsy may

provide effective and tolerable alternatives in the management of seizures (Sun et al., 2023).

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