

Pharmacological Review of Plants and Natural Products with Antiepileptic Effects

Abstract

Epilepsy is a neurological disorder that presents with recurring and spontaneous seizures. It is prevalent worldwide, affecting up to 65 million people, with 80% of cases found in lower-income countries. Medicinal plants are commonly employed for managing and treating epilepsy and convulsions due to their unique therapeutic properties. With increasing research and clinical application, medicinal plants are gaining attention globally due to their potent therapeutic effects and fewer side effects. The development of new plant-based antiepileptic/anticonvulsant agents has become a major focus in the pharmaceutical industry. This article summarizes recent research on medicinal plants with reported antiepileptic/anticonvulsant effects. It provides pharmacological and molecular mechanism of action information for the crude extracts and related active constituents evaluated in preclinical research for the treatment of epilepsy and convulsions, and offers a reference for the development of future related studies in this area. Articles related to ethnopharmacological and antiepileptic studies on plants or natural products from recent and most recent were collected from PubMed, Web of Science and Scopus, etc. using keywords related to epilepsy, medicinal plants, and natural products, etc. Different plant species are commonly used to treat epilepsy and convulsions in African and Asian countries. Also, natural products showing potential for antiepileptic/anticonvulsant effects have been identified from these medicinal plants. These products can be broadly classified as alkaloids, coumarins, flavonoids, saponins, terpenoids and other compounds. The antiepileptic action of plant extracts and their active ingredients can be classified according to their abilities to modulate the GABAergic and glutamatergic systems, act as antioxidants, exhibit anti-neuroinflammatory effects, and provide neuroprotection. In addition, we highlight that some medicinal plants capable of pharmacologically relieving epilepsy and cognition may be therapeutically useful in the treatment of refractory epilepsy. The review highlights the fact that herbal medicinal products used in traditional medicine are a valuable source of potential candidates for antiepileptic drugs. This confirms and encourages the antiepileptic/anticonvulsant activity of certain medicinal plants, which could serve as inspiration for further development. However, the aspects of structural modification and optimization, metabolism, toxicology, mechanisms, and clinical trials are not fully understood and need to be further explored.

Keywords: Epilepsy, Anticonvulsants, Seizures, Natural products

Introduction

Epilepsy, a prevalent chronic neurological disorder, is marked by recurring seizures due to atypical neuronal activity [1]. It is the third most frequent central nervous system (CNS) disorder, causing various nervous system syndromes and leading to neurobiological, cognitive, psychological and social impacts[2]. Epilepsy currently affects more than 65 million people worldwide, with 80% of patients living in poor countries, placing a huge economic burden on families and causing socio-economic and health problems[2]. China, being a developing country, has around 10 million individuals suffering from epilepsy, with new cases emerging each year [3]. In Africa, more than 10 million people suffer from epilepsy and the treatment gap for epilepsy is estimated at 68.5% [4]. Therefore, research into appropriate medical care and treatment for epilepsy will always be a focus and a challenging issue for different countries.

For a long time, the treatment of epilepsy has mainly included medication, surgery, dietary therapy, acupuncture and moxibustion, etc. [5]. Among these, drugs are currently the preferred choice for the management and treatment of epilepsy. Currently, more than fifty different antiepileptic drugs (AEDs), including carbamazepine, oxcarbazepine, sodium valproate, gabapentin, lamotrigine, topiramate, levetiracetam, lacosamide, pregabalin and stiripentol, etc., are available on the world pharmaceutical market[6]. However, 30%–40% of people with epilepsy may experience side effects when using standard AEDs. Besides, nearly 30% of patients are resistant to existing drugs. As a result, there is still an unmet need in the treatment of epilepsy [7]. In addition, long-term use of some AEDs has resulted in adverse effects and the risk of drug-drug interactions which are also the major limitations of the clinical use of AEDs[8]. In fact, drug-resistant epilepsy has become increasingly common in patients taking existing AEDs in

recent years [9]. Therefore, research and development of novel AEDs with multiple targets and low side effects is both urgent and challenging.

1. Types of epileptic seizures

Seizures have two main types, i.e. focal or partial seizures and generalized seizures. In focal seizures, only one part of the brain, occasionally called the 'focus' of the seizures, is affected. Focal seizure may affect a large part of one hemisphere or only a small area of a lobe but generalized seizures occur when seizure activity is widespread in the brain's left and right hemispheres and the affected people become unconscious (except in myoclonic seizures), though for a few seconds [10].

2. Basic mechanisms of epilepsy

Seizure initiation is characterized by two parallel conditions: 1) high-frequency bursts of action potentials, and 2) hyper synchronization of a neuronal population [11].

The bursting activity due to the neuronal membrane's relatively prolonged depolarization occurs because of influx of extracellular Ca^{++} , which results in influx of Na^+ , opening of voltage-dependent Na^+ channels, and generation of repetitive action potentials. The hyperpolarizing potential is mediated by Cl^- influx and gamma-aminobutyric acid (GABA) receptors, or by K^+ efflux, according to the cell type [12]. GABA is a type of the brain's inhibitory neurotransmitter, which effectively prevents the brain from sending messages [12].

GABA interneurons may result in paradoxical facilitation of certain types of epileptic discharges in some models. Drugs that cause increase in synaptic GABA by inhibition of GABA catabolism or reuptake, are considered effective anticonvulsants, including benzodiazepines, which improve GABA binding to the GABA receptor, leading to increased frequency of chloride

channel openings [13]. Some GABA synthesis inhibitors are able to cause seizures, including thiosemicarbazide, 4deoxypyridoxine, isoniazid, and L-allyglycine[13].

GABA, the major inhibitory neurotransmitter, interacts with two key subtypes of receptors: GABA_A and GABA_B. GABA_A receptors are found postsynaptically, but GABA_B receptors are found presynaptically and can therefore modulate synaptic release. GABA_A receptors are permeable to Cl⁻ ions in the brain in adulthood; Cl⁻ influx, upon activation, hyperpolarizes the membrane and inhibits action potentials. Therefore, GABA_A receptor agonists, including barbiturates and benzodiazepines, suppress seizure activity. GABA_B receptors are related to second messenger systems but not Cl⁻ channels, and result in attenuation of transmitter release because of their presynaptic location [13].

Glutamate is a type of amino acid and a major excitatory neurotransmitter in the brain. Glutamate released from synapses is taken up by astrocytes under normal conditions, and is rapidly converted to the non-excitotoxic amino acid glutamine by glutamine synthetase [14].

The ionotropic N-methyl-D-aspartate (NMDA), α-amino-3hydroxy-5-methyl-4-isoxazole propionic acid/kainate, and metabotropic glutamate receptor-mediated mechanisms are involved in epileptic seizures [14].

Excitatory glutamatergic mechanisms are involved in acute, transient, evoked seizures as well as long-term, adaptive cellular plasticity related to epileptogenesis in chronic epilepsy models. Glutamate exerts its excitatory effects through ligand-gated ion channels (NMDA and non-NMDA receptors) in order to increase sodium and calcium conductance [15].

Neuronal (EAAC1) and glial glutamate transporters facilitate reuptake of glutamate and aspartate after synaptic release. Down-regulation of glutamate transporters can be compatible with enhanced excitatory activity [16].

3. Epilepsy and oxidative stress

Oxidative stress leads to cellular damage and functional cellular disruption and can subsequently cause cell death through oxidation of biomolecules such as lipids, proteins, and nucleotides [17].

Seizure generation can be associated with the homeostatic imbalance between antioxidants and oxidants. Oxidative stress has been described as an imbalance between generation and elimination of reactive oxygen species (ROS) and reactive nitrogen species [18].

ROS levels are relatively well regulated to do significant functions including autophagy, cell division, chemical signaling, and mitogen-activated protein kinase signaling and apoptosis. Because of the highly reactive nature of this molecule, the ROS is tightly regulated. ROS-induced mitochondrial dysfunction is frequently seen following seizures throughout epileptogenesis[19].

Epileptic seizure causes initiation of remarkable influx of calcium through voltage-gated and NMDA-dependent ion channels that escalate intracellular ions and bring about biochemical cascades. High levels of intracellular calcium can induce ROS [20]. ROS may be scavenged by certain enzymatic antioxidant defense systems such as superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase, and peroxiredoxins and non-enzymatic ones such as vitamin C, vitamin E, and reduced glutathione (GSH) [21]. Antioxidant therapies to reduce oxidative stress have attracted much attention in treatment for epilepsy.

4. Epilepsy and inflammation

Experimental findings in rodents have indicated that seizures cause inflammatory mediators to increase in brain regions involved in generating epileptic activity [22]. Direct antiinflammatory

treatments have been found to suppress some types of epileptic seizures. Inflammatory processes may occur prior to the onset of epilepsy in humans, potentially contributing etiopathogenetically to incidence of spontaneous seizures. A rapid-onset inflammatory response is triggered in glia by seizures that have been induced by chemoconvulsants or electrical stimulation [23].

The over-expressing cytokines, e.g. interleukin-6 (IL-6) and tumor necrosis factor- α , inside astrocytes have been reported to cause age-dependent neurological dysfunctions such as decreased seizure threshold and spontaneous seizure frequency [24].

Inflammatory cytokines such as IL-1 β and high-mobility group box 1, activate IL-1 receptor type I and Toll-like receptor 4, respectively. IL-1 receptor/Toll-like receptor signaling can regulate neuronal excitability, including inhibition of Ca²⁺ channels outward current, alteration of synaptic transmission, and decrease in GABA production [25].

5. Antiepileptic drugs

Most epileptic seizures are controlled by drug therapy, especially anticonvulsants [26]. Treatments for seizures are based on anticonvulsant medication, although there are various choices of anticonvulsant drugs with different seizure types and epileptic syndromes [27]. Patients with newly diagnosed epilepsy who need treatment can start treatment with standard anticonvulsants including carbamazepine, valproic acid/valproate semisodium, phenytoin, phenobarbital, or more recently with gabapentin, oxcarbazepine, lamotrigine, or topiramate [28].

The type of prescribed treatment depends on different factors including the severity and frequency of the seizures as well as age, overall health, and medical history. Accurate diagnosis of epilepsy type is essential to choose the best treatment [28].

Conventional antiepileptic drugs may block sodium channels or improve GABA function. Different antiepileptic drugs have multiple or uncertain mechanisms of action [29]. Next to the voltage-gated sodium channels and components of the GABA system, their targets include GABA_A receptors, the GABA transporter 1, and GABA transaminase. Other targets include voltage-gated calcium channels, SV2A, and $\alpha_2\delta$ [30].

Through blocking sodium or calcium channels, antiepileptic drugs decrease the release of excitatory glutamate, which increases in epilepsy, and also GABA [31]. This is possibly a side effect or the actual action mechanism of some of the antiepileptic drugs, because GABA can directly or indirectly act proconvulsively [32].

Most of the drugs currently being used have unpleasant side effects and unpredictable pharmacological actions; therefore, it is necessary to search for newer drugs with fewer or no side effects and predictable pharmacological action because treatment of epilepsy is a long-term process and drug taking is discontinued gradually for about six months [32].

The plant kingdom is a valuable resource for finding new structural types of AEDs. Indeed, the world's traditional medicine has a long history and rich practical experience in the treatment of epilepsy. The medicinal use of plants for the treatment of epilepsy has been documented since ancient times [33]. In particular, herbal medicine has been used internationally as a complementary or alternative medicine for the treatment of epilepsy, and medicinal plants for epilepsy are often considered a mild and safe alternative to chemical AEDs [34]. In ancient China, doctors did not have a precise name for epilepsy [35]. In the "Prescriptions of Fifty-two Diseases" and "QianjinYaofang", patients were named "horse epilepsy", "cow epilepsy", "dog epilepsy", "sheep epilepsy", "snake epilepsy", etc., based on the patient's abnormal posture, stance and abnormal sounds during seizures. In Traditional Chinese Medicine (TCM), epilepsy is

called “Dian”, “Xian”, “Dian Kuang”, “Yangjiao Feng”, “Zao Kuang” and convulsions, [2]. Thousands of years of TCM culture have accumulated valuable clinical experience and developed various treatment methods, such as herbal medicine, acupuncture therapy, moxibustion therapy, tuina, emotional adjustment therapy, etc.[2]. The earliest evidence for the use of medicinal plants in the treatment of epilepsy was recorded in Huangdi’s Classic of Medicine two thousand years ago. After thousands of years of clinical practice, a lot of valuable experience has been accumulated, and a large number of classic prescriptions with confirmed effects have been invented based on TCM theories. Some of these herbal preparations recorded in history are still in use today. At present, more than 20 Chinese patent medicines composed of herbs have been made for clinical use[2].

In addition, herbal treatments are extensively used in traditional medicine as infusion or decoction for epileptic patients in Japan, Korea, Australia, India and Mexico, as well as African and South American countries, etc.[36]. The leaves, roots and/or bark of medicinal plants prescribed by traditional medical healers are taken orally or used as a bath to treat convulsions [37]. For example, the decoction of *Margaritariadiscoidea* (Baill.) G.L.Webster, *Dalbergia boehmii* Taub., *D. nitidula* Welwex Baker, *Catunaregam spinosa* (Thunb.) Tirveng., and *Lannea discolor* (Sond.) Engl. are widely used in Africa to treat convulsions [37].

Over the last five years, a large number of compounds from medicinal plants have been found to have significant antiepileptic activity. For example, the antiepileptic/anticonvulsant option of cannabidiol (CBD) from the genus *Cannabis* has been confirmed by results from animal models and human trials, and cannabidiol-enriched medicinal cannabis has been used clinically as an adjunctive therapy for the treatment of refractory epilepsy in children and[38]. The active ingredient of *Acorus tatarinowii* Schott, asarone, is manufactured into capsules for the treatment

of grand mal epilepsy and has been approved by the China Food and Drug Administration (CFDA) [39].

However, the review that primarily focuses on pharmacological screening and mechanism exploration of individual isolates and crude extracts is limited[2]. In addition, over the past five years, there has been an increase in research into medicinal herbs and botanicals for their anti-epileptic properties. There is still a lack of information on the phytoconstituents and medicinal plants, as well as their toxicities and applications in the last five years, which may hinder the better utilization of these medicinal herbs[40]. Therefore, in this review, we present a comprehensive outlook of some medicinal plants and natural products with antiepileptic potential, highlighting the ethnomedicinal use, phytoconstituents, pharmacology and mechanisms they imply, as well as clinical investigation. This review will provide a repository of antiepileptic plants for future investigation and also provide new concepts for better research and discovery of new plant-derived AEDs.

Ethnomedicinal uses

From ancient times to the present, a large number of medicinal plants have been used in many countries for the treatment of convulsions, epilepsy and other CNS-related disorders[41]. As shown in Table 1, the whole plants, fruits, leaves, seeds, roots and stem barks have been processed as decoctions or other forms of administration in traditional medicine. In particular, the crude extracts of these plants has been reported to improve and attenuate seizure

Medicinal plants and natural products against epileptic seizures

Extensive in vivo research has demonstrated the antiepileptic and anticonvulsant properties of various medicinal plants. This section specifically examines the antiepileptic and anticonvulsant effects of the crude extracts and active ingredients isolated from different medicinal species in scientific literature (refer to Table 1). Notably, the antiepileptic/anticonvulsant efficacy of these medicinal plants and constituents has been confirmed by various epileptic

Table 1: Antiepileptic medicinal plants or natural products

Plants/Natural products	Methods (induced seizures)	Mechanism of action	Reference
Ficus platyphylla methanol extract	PTZ (37.5 mg/kg) i.p. for a total of 13 convulsant injections in mice, learning performance was tested in a two-way shuttlebox	Affinity for undifferentiated glutamate receptors, affinity for the 3H-GABA binding assay, decrease the K ⁺ -stimulated glutamate release from rat hippocampal slices	[42]
Psidium guajava (guava) leaves ethanolic extract	Delivering electroshock (50 mA) for 0.2 s through a pair of ear clip electrodes and PTZ (70 mg/kg) i.p. injection induces tonic-clonic convulsions in mice	Selectively inhibit NMDA receptor	[43]
Trachyspermum mammi (L.) methanol extract	Strychnine (4 mg/kg) i.p. injection-induced seizure in rats	Excite GABA responses mainly by stimulating human GABA _A receptors and increasing the chloride ion channel opening	[44]
Zhumeriamajdae essential oil and methanolic extract	PTZ (110 mg/kg) and MES models in mice	Inhibit voltage-dependent Na ⁺ channels, block glutamatergic excitation mediated by the NMDA receptor	[45]
Acorus calamus Linn aqueous extract	PTZ (80 mg/kg) and MES models in mice	Block NMDA receptors	[46]
Vitexin (a flavonoid)	Vitexin administered intracerebroventricularly, administered PTZ (90 mg/kg i.p.)	Vitexin is a ligand for benzodiazepine receptors, exerts anticonvulsant effects through a GABA _A benzodiazepine receptor	[47]
Anisomeles malabarica (flavonoids fraction from the leaves)	MES, administered PTZ (50 mg/kg) in rat	Decreased tonic hindlimb extension phase and extensor/flexion ratio in MES model	[48]

Angelica archangelica Linn. roots essential oil	PTZ (80 mg/kg) and MES models in mice	Block glutamatergic excitation	[49]	PTZ: Pentylene tetrazole; MES: Maximal electroshock; MDA: Malondialdehyde; AChE: Acetylcholinesterase; BChE: Butyryl cholinesterase
Cymbopogon winterianus Jowitt essential oils	Pilocarpine-induced convulsions (350 mg/kg i.p.) administrated PTZ in mice	GABAergic mechanisms, deteriorated autoregulation of glutamate release	[50]	
Mentha spicata essential oils	Administrated PTZ (80 mg/kg) in mice	GABAergic mechanisms	[51]	
Trichosanthes dioica Roxb fruits aqueous extract	Delivering electroshock (50 mA) for 0.2 s through a pair of ear clip electrodes, PTZ (80 mg/kg) i.p. injection induces tonic-clonic convulsions in mice	Activity against generalized tonic-clonic and cortical focal seizures	[52]	
Lavandula angustifolia essential oils	Administrated PTZ (80 mg/kg) in mice	Modulate glutamate activation expression, reduction of the ACh-evoked release, direct interaction with the NMDA receptor complex	[53]	

terase; ACh: Acetylcholine.

Discussion

Ficus platyphylla methanol extract: Decoctions of *Ficus platyphylla* are used in Nigeria's folk medicine to manage epilepsy for many years and their efficacies are widely acclaimed among the rural communities of Northern Nigeria[54]. The study examined the ameliorative effects of the standardized methanol extract of *Ficus platyphylla* stem bark on seizure severity, cognitive deficit and neuronal cell loss in pentylenetetrazole-kindled mice. The (35) S-GTP γ S, glutamate and γ -aminobutyric acid receptors binding properties of the extract were also evaluated. Male CD-1 mice were kindled with an initial subeffective dose of pentylenetetrazole (PTZ, 37.5mg/kg, i.p.) for a total of 13 convulsant injections and the treatment groups concurrently received *Ficus platyphylla* (100 and 200mg/kg)[42]. Control animals received the same number of saline injections. Twenty-four hours after kindling completion the animals' learning performance was tested in a two-way shuttle-box. The animals were challenged with another subeffective dose of PTZ (32.5mg/kg, i.p.) on day 7 after kindling completion. Animals were sacrificed a day after the challenged experiment and the brains were processed for histological investigation. FP

ameliorates seizure severity, cognitive deficits and neuronal cell loss in PTZ kindled mice. Components of the extract showed affinity for GABAergic and glutamatergic receptors. Glutamate release was diminished and the (35) S-GTP γ S binding assay revealed no intrinsic activity at glutamatergic receptors. The results revealed that *Ficus plathyphylla* contains psychoactive secondary metabolites with anticonvulsant properties, thus supporting the isolation and development of the biologically active components of this medicinal plant as antiepileptic agents[42].

Psidium guajava (guava) leaves ethanolic extract: The anticonvulsant activity of ethanolic extract (200mg/kg & 400mg/kg) of *Psidium guajava* (guava leaves) in albino mice.

Albino mice (25-30gms) of either sex were randomly selected and divided into 4 groups of 6 mice each, Group I (control) – Distilled water (vehicle) 1ml, Group II (Standard) – Valproic acid (40mg/kg), Group III T1, ethanolic extract of *Psidium guajava* (200mg/kg), Group IVT2, ethanolic extract of *Psidium guajava* (400mg/kg)[55]. All drugs were administered orally 1 h before the induction of seizures. The anticonvulsant activity was screened using maximal electroshock (MES) and pentylenetetrazole (PTZ) models[56].

It was found out the ethanol extract of *Psidium guajava* dose-dependently produced significant antiepileptic activity in comparison to control. In MES test, the percentage inhibition of seizure is T2 49% and T1 – 37% in comparison to control. In the PTZ test, the percentage of protection from seizure by T2 is 83.4%, and T1 is 50% when compared to the standard drug.

The findings showed the ethanol extract of *Psidium guavajava* leaves showed significant anticonvulsant activity at a higher dose of 400 mg[57].

Trachyspermum mammi (L.) was tested utilizing a single- and multiple-dosing schedule in an epileptic model caused by strychnine[58]. Three groups of twenty-one animals each were given a vehicle as the control, diazepam as the standard, and Trachyspermum mammi (L.) extract as the test. Since there was a highly significant delay in the beginning of convulsions compared to the control, and since a higher percentage of animals survived or ignored seizure than the control, Trachyspermum mammi (L.) was shown to have antiepileptic effects[59]. But when compared to the control, the duration of convulsions was much longer when using both diazepam and Trachyspermum mammi (L.). Thymol may have contributed to the antiepileptic action of the Trachyspermum mammi (L.) methanol extract[58].

The anticonvulsant properties of Zhumeriamajdae's essential oil (ZMEO) and methanolic extract (ZMME) in mouse models of maximum electroshock (MES) and pentylenetetrazol (PTZ) was studied. ZMEO and ZMME were administered in varying doses to mice half an hour before to the development of chemical and electrical convulsions[60]. The Rota-rod test was used to assess neurotoxicity, which includes sedation and movement toxicity. The mortality was assessed 24 hours after injecting varying dosages of ZMEO and ZMME. The results obtained indicate that mice were protected against tonic convulsions caused by PTZ and MES with effective doses (ED_{50}) of 0.26 (0.13–0.39) and 0.27 (0.17–0.37) ml/kg, respectively, by ZMEO in a dose-dependent manner[61]. The study showed that Z. majdae essential oil is a promising subject for more anticonvulsive research[61].

Vitexin has been shown to have protective effects as an antioxidant against reactive oxygen species, lipid peroxidation, and other oxidative damages in various diseases related to oxidative stress[62]. These diseases include seizure, memory impairment, cerebral ischemia, neurotoxicity, myocardial and respiratory injury, and metabolic dysfunction. The protective effects are believed

to be due to molecular and cellular mechanisms. This review examines the impact of vitexin's antioxidant action on the activation or inhibition of signaling pathways[63].

The ethyl acetate extract (2.12% w/w) of the leaves of *Anisomelesmalabarica* was prepared and fractionated into total flavonoids fraction (AMFF) and tannins fraction (AMTF), which subsequently evaluated for the antiepileptic activity against PTZ- and MES model in wistar rats[64]. Diazepam and phenytoin (2 mg/kg and 25 mg/kg, i.p., respectively), were used as a reference drugs. Single dose pretreatment with AMFF (25 and 50 mg/kg, i.p.) has found to be effective against both MES and PTZ-convulsions, but associated with a marked decrease in locomotor activity and motor activity performance (i.e., neurotoxic effects), similar to that of diazepam treatment. Interestingly, chronic treatment with AMFF at lower doses (6.25 and 12.5 mg/kg, i.p., 1 week) has also produced significant antiepileptic activity, but without causing neurotoxic effects[65].

Thus, this study concluded that the flavonoids fraction of the EA extract of *Anisomelesmalabarica* leaves has antiepileptic potential against both MES and PTZ convulsion models[65].

The efficacy of *Angelica archangelica*Linn., root essential oil was assessed in the treatment of seizures caused by electrical and chemical means[49]. The seizures in mice were provoked using maximum electroshock and pentylenetetrazol. A comparative analysis was conducted to assess the impact of *Angelica archangelica* root essential oil on seizures, in comparison to the conventional anticonvulsant medications, phenytoin and diazepam. The root essential oil of *Angelica archangelica* reduced the length of tonic convulsions and showed improvement in maximum electroshock-caused seizures. Additionally, it delayed the beginning of clonic convulsions and protected against mortality in pentylenetetrazol-induced seizures[66].

Conclusion : research on the active ingredients in plant-based extracts and natural products may be crucial to determining the chemical components needed to create antiepileptic medications in the future.

Reference

1. Lattanzi S, Zaccara G, Giovannelli F, Grillo E, Nardone R, Silvestrini M, Trinkka E, Brigo F: **Antiepileptic monotherapy in newly diagnosed focal epilepsy. A network meta-analysis.***Acta neurologica Scandinavica* (2019) **139**(1):33-41.
2. He X, Chen X, Yang Y, Xie Y, Liu Y: **Medicinal plants for epileptic seizures: Phytoconstituents, pharmacology and mechanisms revisited.***Journal of ethnopharmacology* (2024) **320**(117386).
3. Ding D, Zhou D, Sander JW, Wang W, Li S, Hong Z: **Epilepsy in china: Major progress in the past two decades.***The Lancet Neurology* (2021) **20**(4):316-326.
4. Nicholas A: **Unlocking the hidden burden of epilepsy in africa: Understanding the challenges and harnessing opportunities for improved care.***Health science reports* (2023) **6**(4):e1220.
5. Verrotti A, Iapadre G, Di Francesco L: **Diet in the treatment of epilepsy: What we know so far.** (2020) **12**(9).
6. Perucca E: **The pharmacological treatment of epilepsy: Recent advances and future perspectives.***Acta Epileptologica* (2021) **3**(1):22.
7. Ioannou P, Foster DL, Sander JW, Dupont S, Gil-Nagel A, Drogon O'Flaherty E, Alvarez-Baron E, Medjedovic J: **The burden of epilepsy and unmet need in people with focal seizures.***Brain and behavior* (2022) **12**(9):e2589.
8. Park KM, Kim SE, Lee BI: **Antiepileptic drug therapy in patients with drug-resistant epilepsy.***Journal of epilepsy research* (2019) **9**(1):14-26.
9. Guery D, Rheims S: **Clinical management of drug resistant epilepsy: A review on current strategies.** (2021) **17**(2229-2242).

10. Sarmast ST, Abdullahi AM, Jahan N: **Current classification of seizures and epilepsies: Scope, limitations and recommendations for future action.***Cureus* (2020) **12**(9):e10549.
11. Geng H, Chen X, Wang C: **Systematic elucidation of the pharmacological mechanisms of rhynchophylline for treating epilepsy via network pharmacology.***BMC Complementary Medicine and Therapies* (2021) **21**(1):9.
12. Knowles JK, Helbig I: **Precision medicine for genetic epilepsy on the horizon: Recent advances, present challenges, and suggestions for continued progress.** (2022) **63**(10):2461-2475.
13. Ngo DH, Vo TS: **An updated review on pharmaceutical properties of gamma-aminobutyric acid.***Molecules (Basel, Switzerland)* (2019) **24**(15).
14. Li C, Huang L, Jia X, Zhao B, Chen L, Liu Y: **Functional glutamate transporters are expressed in the carotid chemoreceptor.** (2020) **21**(1):208.
15. Sumadewi KT, Harkitasari S, Tjandra DC: **Biomolecular mechanisms of epileptic seizures and epilepsy: A review.***Acta Epileptologica* (2023) **5**(1):28.
16. Todd AC, Hardingham GE: **The regulation of astrocytic glutamate transporters in health and neurodegenerative diseases.** (2020) **21**(24).
17. Łukawski K, Czuczwar SJ: **Oxidative stress and neurodegeneration in animal models of seizures and epilepsy.***Antioxidants* (2023) **12**(5).
18. Madireddy S, Madireddy S: **Therapeutic strategies to ameliorate neuronal damage in epilepsy by regulating oxidative stress, mitochondrial dysfunction, and neuroinflammation.***Brain sciences* (2023) **13**(5).
19. Borowicz-Reutt KK, Czuczwar SJ: **Role of oxidative stress in epileptogenesis and potential implications for therapy.***Pharmacological reports : PR* (2020) **72**(5):1218-1226.
20. Eastman CL, D'Ambrosio R, Ganesh T: **Modulating neuroinflammation and oxidative stress to prevent epilepsy and improve outcomes after traumatic brain injury.***Neuropharmacology* (2020) **172**(107907).

21. Jomova K, Raptova R, Alomar SY, Alwasel SH, Nepovimova E, Kuca K, Valko M: **Reactive oxygen species, toxicity, oxidative stress, and antioxidants: Chronic diseases and aging.** (2023) *97*(10):2499-2574.
22. Golub VM, Reddy DS: **Post-traumatic epilepsy and comorbidities: Advanced models, molecular mechanisms, biomarkers, and novel therapeutic interventions.***Pharmacological reviews* (2022) *74*(2):387-438.
23. Fu M, Zhu Y, Zhang J, Wu W, Sun Y, Zhang X, Tao J, Li Z: **Microrna-221-3p suppresses the microglia activation and seizures by inhibiting of hif-1 α in valproic acid-resistant epilepsy.***Frontiers in pharmacology* (2021) *12*(714556).
24. Çarçak N, Onat F, Sitnikova E: **Astrocytes as a target for therapeutic strategies in epilepsy: Current insights.***Frontiers in molecular neuroscience* (2023) *16*(1183775).
25. Kobylarek D, Iwanowski P, Lewandowska Z, Limphaibool N, Szafranek S, Labrzycka A, Kozubski W: **Advances in the potential biomarkers of epilepsy.***Frontiers in neurology* (2019) *10*(685).
26. Ramakrishnan S, Singh T, Reddy DS: **Protective activity of novel hydrophilic synthetic neurosteroids on organophosphate status epilepticus-induced chronic epileptic seizures, non-convulsive discharges, high-frequency oscillations, and electrographic ictal biomarkers.** (2024) *388*(2):386-398.
27. Hakami T: **Neuropharmacology of antiseizure drugs.***Neuropsychopharmacology reports* (2021) *41*(3):336-351.
28. Nevitt SJ, Sudell M, Cividini S, Marson AG, Tudur Smith C: **Antiepileptic drug monotherapy for epilepsy: A network meta-analysis of individual participant data.***The Cochrane database of systematic reviews* (2022) *4*(4):Cd011412.
29. Löscher W, Klein P: **The pharmacology and clinical efficacy of antiseizure medications: From bromide salts to cenobamate and beyond.***CNS Drugs* (2021) *35*(9):935-963.
30. Dolphin AC: **Voltage-gated calcium channels: Their discovery, function and importance as drug targets.***Brain and neuroscience advances* (2018) *2*(
31. Green JL, Dos Santos WF, Fontana ACK: **Role of glutamate excitotoxicity and glutamate transporter eaat2 in epilepsy: Opportunities for novel therapeutics development.***Biochem Pharmacol* (2021) *193*(114786).

32. Sills GJ, Rogawski MA: **Mechanisms of action of currently used antiseizure drugs.***Neuropharmacology* (2020) **168**(107966).
33. Li H, Huang C, Li Y, Wang P, Sun J, Bi Z, Xia S, Xiong Y, Bai X, Huang X: **Ethnobotanical study of medicinal plants used by the yi people in mile, yunnan, china.***Journal of ethnobiology and ethnomedicine* (2024) **20**(1):22.
34. Zhu Z, Dluzynski D, Hammad N, Pugalenthi D, Walser SA: **Use of integrative, complementary, and alternative medicine in children with epilepsy: A global scoping review.** (2023) **10**(4).
35. Kaculini CM, Tate-Looney AJ, Seifi A: **The history of epilepsy: From ancient mystery to modern misconception.***Cureus* (2021) **13**(3):e13953.
36. Salm S, Rutz J, van den Akker M, Blaheta RA, Bachmeier BE: **Current state of research on the clinical benefits of herbal medicines for non-life-threatening ailments.***Frontiers in pharmacology* (2023) **14**(1234701).
37. Alhazmi HA, Najmi A, Javed SA, Sultana S, Al Bratty M, Makeen HA, Meraya AM, Ahsan W, Mohan S, Taha MME, Khalid A: **Medicinal plants and isolated molecules demonstrating immunomodulation activity as potential alternative therapies for viral diseases including covid-19.***Frontiers in immunology* (2021) **12**(637553).
38. Espinosa-Jovel C: **Cannabinoids in epilepsy: Clinical efficacy and pharmacological considerations.***Neurología (English Edition)* (2023) **38**(1):47-53.
39. Wang M, Tang HP, Wang S, Hu WJ, Li JY, Yu AQ, Bai QX, Yang BY, Kuang HX: **Acorus tatarinowii schott: A review of its botany, traditional uses, phytochemistry, and pharmacology.***Molecules (Basel, Switzerland)* (2023) **28**(11).
40. Kumar A, P N: **Major phytochemicals: Recent advances in health benefits and extraction method.** (2023) **28**(2).
41. Birhan YS: **Medicinal plants utilized in the management of epilepsy in ethiopia: Ethnobotany, pharmacology and phytochemistry.***Chinese Medicine* (2022) **17**(1):129.
42. Chindo BA, Schröder H, Becker A: **Methanol extract of ficus platyphylla ameliorates seizure severity, cognitive deficit and neuronal cell loss in pentylenetetrazole-kindled mice.***Phytomedicine : international journal of phytotherapy and phytopharmacology* (2015) **22**(1):86-93.

43. Pushpa VH, Shetty KP, Sushma N, Kalabharathi HL, Satish AM: **Evaluation of the anticonvulsant activity of ethanol extract of *Psidium guajava* (guava leaves) in albino mice.**
44. Eftekhari M, Hoseinsalari A, Mansourian M, Farjadmand F, Shams Ardekani MR, Sharifzadeh M, Hassanzadeh G, Khanavi M, Gholami M: **Trachyspermum ammi (L.) sprague, superb essential oil and its major components on peptic ulcers: In vivo combined in silico studies.** *DARU Journal of Pharmaceutical Sciences* (2019) **27**(1):317-327.
45. Khosravi K, Monajemi Mamaghani A, Hosseinzadeh H: **Pharmacological and toxicity effects of *Zhumeria majdae* and its bioactive constituents: A review.** *Iranian journal of basic medical sciences* (2023) **26**(3):255-268.
46. Sharma V, Sharma R, Gautam DS, Kuca K, Nepovimova E, Martins N: **Role of vacha (*Acorus calamus* Linn.) in neurological and metabolic disorders: Evidence from ethnopharmacology, phytochemistry, pharmacology and clinical study.** *Journal of clinical medicine* (2020) **9**(4).
47. Sharma P, Kumar A, Singh D: **Dietary flavonoids interaction with creb-bdnf pathway: An unconventional approach for comprehensive management of epilepsy.** *Current neuropharmacology* (2019) **17**(12):1158-1175.
48. Choudhary N, Bijjem KRV, Kalia AN: **Antiepileptic potential of flavonoids fraction from the leaves of *Anisomeles malabarica*.** *Journal of ethnopharmacology* (2011) **135**(2):238-242.
49. Pathak S, Wanjari MM, Jain SK, Tripathi M: **Evaluation of antiseizure activity of essential oil from roots of *Angelica archangelica* Linn. in mice.** *Indian journal of pharmaceutical sciences* (2010) **72**(3):371-375.
50. Rabiei Z: **Anticonvulsant effects of medicinal plants with emphasis on mechanisms of action.** *Asian Pacific Journal of Tropical Biomedicine* (2017) **7**(2):166-172.
51. El Menyiy N, Mrabti HN: **Medicinal uses, phytochemistry, pharmacology, and toxicology of *Mentha spicata*.** (2022) **2022**(7990508).
52. Khandaker M, Akter S, Imam MZ: ***Trichosanthes dioica* Roxb.: A vegetable with diverse pharmacological properties.** *Food Science and Human Wellness* (2018) **7**(1):34-48.

53. Bahr TA, Rodriguez D, Beaumont C, Allred K: **The effects of various essential oils on epilepsy and acute seizure: A systematic review.** (2019) **2019**(6216745).
54. Chindo BA, Amos S, Odutola AA, Vongtau HO, Abbah J, Wambebe C, Gamaniel KS: **Central nervous system activity of the methanol extract of ficus platyphylla stem bark.***Journal of ethnopharmacology* (2003) **85**(1):131-137.
55. Manu G, Padmanabha ST, Chandrakantha T, Ravishankar M: **Evaluation of anticonvulsant activity of ethanolic extract of leaves of ocimum sanctum (tulsi) in albino rats.***National Journal of Physiology, Pharmacy and Pharmacology* (2017) **7**(762-765).
56. Fisseha N, Hammeso WW, Nureye D: **Anticonvulsant activity of hydro alcoholic extract and solvent fractions of biophytum umbraculum welw. Syn (oxalidaceae) root in mice.***Journal of Experimental Pharmacology* (2022) **14**(null):291-299.
57. Kumar M, Tomar M, Amarowicz R: **Guava (psidium guajava L.) leaves: Nutritional composition, phytochemical profile, and health-promoting bioactivities.** (2021) **10**(4).
58. Asif HM, Sultana S, Akhtar N: **A panoramic view on phytochemical, nutritional, ethanobotanical uses and pharmacological values of trachyspermum ammi linn.***Asian Pacific Journal of Tropical Biomedicine* (2014) **4**(S545-S553).
59. Bairwa R, Sodha RS, Rajawat BS: **Trachyspermum ammi.***Pharmacognosy reviews* (2012) **6**(11):56-60.
60. Mandegary A, Sharififar F, Abdar M, Arab-Nozari M: **Anticonvulsant activity and toxicity of essential oil and methanolic extract of zhumeria majdae rech, a unique iranian plant in mice.***Neurochemical research* (2012) **37**(12):2725-2730.
61. Shan HM, Maurer MA, Schwab ME: **Four-parameter analysis in modified rotarod test for detecting minor motor deficits in mice.***BMC biology* (2023) **21**(1):177.
62. Babaei F, Moafizad A, Darvishvand Z, Mirzababaei M, Hosseinzadeh H: **Review of the effects of vitexin in oxidative stress-related diseases.** (2020) **8**(6):2569-2580.
63. Mustapha M, Mat Taib CN: **Beneficial role of vitexin in parkinson's disease.***The Malaysian journal of medical sciences : MJMS* (2023) **30**(2):8-25.

64. Liu X-m, Liu Y, Shan C-h, Yang X-q, Zhang Q, Xu N, Xu L-y, Song W: **Effects of five extraction methods on total content, composition, and stability of flavonoids in jujube.***Food Chemistry: X* (2022) **14**(100287).
65. Choudhary N, Bijjem KR, Kalia AN: **Antiepileptic potential of flavonoids fraction from the leaves of anisomeles malabarica.***J Ethnopharmacol* (2011) **135**(2):238-242.
66. Prakash B, Singh P, Goni R, Raina AKP, Dubey NK: **Efficacy of angelica archangelica essential oil, phenyl ethyl alcohol and α - terpineol against isolated molds from walnut and their antiaflatoxic and antioxidant activity.***Journal of food science and technology* (2015) **52**(4):2220-2228.

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