Herbal and Natural Compounds in Neuropharmacology: Biochemical Innovations of Biomolecules Used to Treat Epilepsy

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Abstract:

A persistent neurological condition called epilepsy is typified by frequent, unplanned seizures brought on by aberrant brain electrical activity. Neuronal hyperexcitability and hypersynchrony are part of its pathogenesis and are frequently brought on by infections, birth abnormalities, brain trauma, or genetic alterations. Common indications and symptoms include convulsions, unconsciousness, anomalies of the senses, and behavioral disorders. The main diagnostic methods include clinical examination, electroencephalography (EEG), and neuroimaging techniques including magnetic resonance imaging (MRI). Common treatment options include vagus nerve stimulation, antiepileptic medications (AEDs), surgery, and nutritional therapy, including the ketogenic diet. Despite these choices, a significant number of people have drug-resistant epilepsy, highlighting the necessity for alternate therapies. Natural substances have drawn attention due to their possible anticonvulsant and neuroprotective qualities. Tanshinone IIA, curcumin, chrysin, apigenin, wogonin, quercetin, carvone, hesperidin, nantenine, osthole, genistein, piperine, triptolide, α-asarone, catechin, baicalin, naringin, vitexin, kaempferol, and fisetin have all showed encouraging preclinical findings.These phytochemicals have anticonvulsant properties because they alter GABAergic transmission, control ion channels, lessen neuroinflammation, and reduce oxidative stress. Their low toxicity and blood-brain barrier crossing make them attractive options for additional or alternative epilepsy therapy. To further understand their mechanisms, improve formulations, and show their value in clinical trials, more study is required.

Keywords: Pathogenesis, diagnosis, oxidative stress, GABA modulation, natural substances, antiepileptic medications, epilepsy, seizures, and neuroprotection. Herbal remedies Curcumin, Chrysin, Apigenin, Wogonin, Quercetin, Carvone, Hesperidin, Nantenine,

Osthole, Genistein, Piperine, Triptolide, α-Asarone, Catechin, Baicalin, Naringin, Vitexin, Kaempferol, and Fisetin are constituents of Tanshinone IIA.

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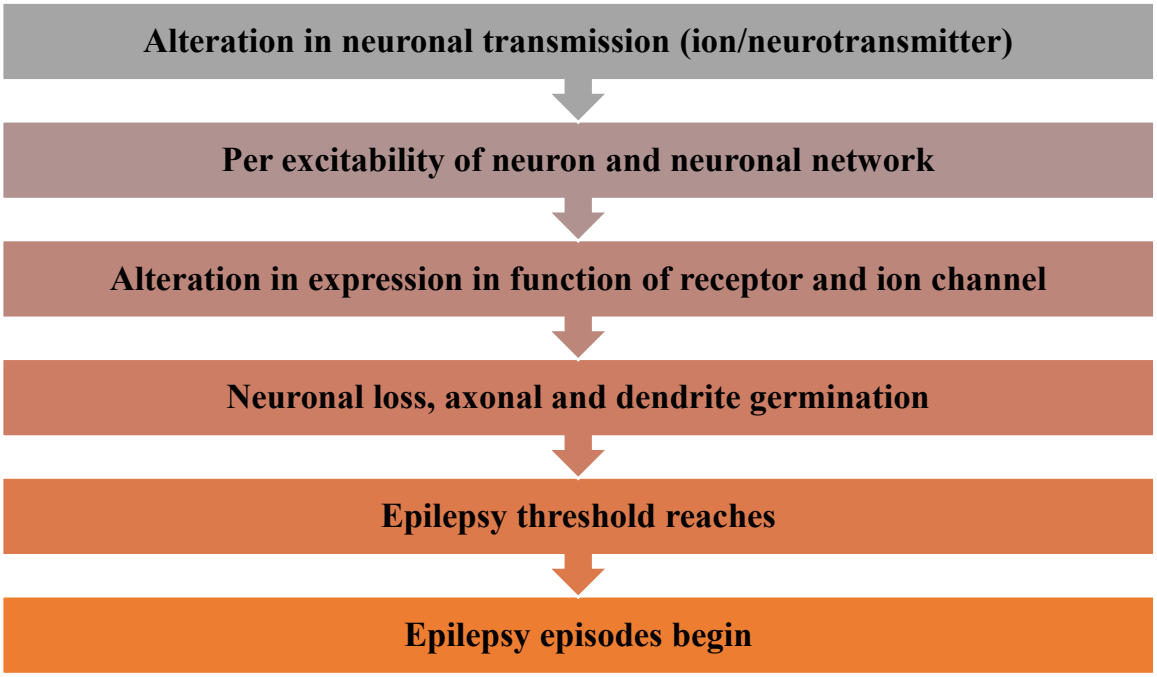
Introduction

Epilepsy, also referred to as “Goatopathy,” was first officially recognized in 1997. Since then, the Global Campaign Against Epilepsy (GCAE) has been dedicated to enhancing access to care, treatment, services, and prevention efforts for epilepsy across the world [1]. According to World Health Organization data from 2006 to 2015, the prevalence of epilepsy has remained consistently high. It is a widespread, serious, and chronic neurological disorder that impacts over 70 million people globally. Epilepsy affects individuals of all ages, genders, ethnicities, and geographic regions [2]. The known causes of epilepsy have been reclassified into six categories: hereditary, structural, infectious, immunological, metabolic, and unknown [3]. There is growing focus on epilepsy treatment, with a combined approach using both Chinese and Western medicine increasingly gaining preference [4]. On one hand, Western medical treatments for epilepsy are primarily categorized into etiological treatment, pharmacological therapy, and surgical intervention—for example, the use of drugs such as levetiracetam, phenytoin sodium, and carbamazepine. On the other hand, natural medicines have also been reported to play a significant role in the clinical management of epilepsy, largely due to the therapeutic activities of their active constituent [5],[6]. Research shows that individuals with epilepsy often face challenges in securing and keeping steady employment. Multiple studies have supported the notion that unemployment and underemployment rates are typically higher among people with epilepsy compared to the general population [7],[8]. Employment plays a crucial role in an individual's overall quality of life. Having a job and earning an income are outward indicators of social integration and acceptance within the community.[9]

Beyond its financial benefits, employment also enhances a person's sense of status, identity, and self-esteem. [10]. For over thirty years, employment has been acknowledged as a major area of difficulty for individuals living with epilepsy.[11]. Individuals with epilepsy face tangible limitations, such as restrictions on driving or working in environments where there's a risk of causing harm. Additionally, they frequently encounter ignorance and stigma, particularly in societies where epilepsy carries negative cultural association. [12], [13]. Natural remedies typically have minimal or no toxic side effects. Moreover, since animals generally do not develop drug resistance, the use of natural drugs in veterinary care often leaves no residue and poses little risk to health. Compared to conventional antiepileptic medications, natural treatments have more complex compositions. While a single natural drug may not achieve a high cure rate, it usually causes only mild side effects, helping to minimize patient discomfort. Combining natural remedies with conventional medications may not only lessen adverse reactions but also enhance overall treatment effectiveness.[14]. Additionally, we have taken an innovative approach by summarizing the combined use of natural drug monomers, natural compound formulations, and conventional antiepileptic drugs. Our goal is to offer new hope to individuals with epilepsy and provide a reliable reference for enhancing treatment outcomes and improving the cure rate.

Fig.1. Epilepsy in Brain

Pathophysiology:



One of the primary causes of epileptic seizures is thought to be the abnormal activity of cortical neurons. This irregular neuronal discharge is largely associated with the loss of specific inhibitory and excitatory neurons in certain brain regions, imbalances in neurotransmitter signalling, synaptic reorganization, axonal sprouting, and alterations in both the structure and function of glial cells. In this context, glial cells and axons within the white matter may serve a secondary, yet contributing, role.[15]. Recurrent seizures can cause changes in synaptic protein expression, trigger synaptic remodelling, and lead to the formation of abnormal neuronal networks factors that are considered key pathophysiological mechanisms underlying refractory epilepsy.[16].Furthermore, advancements in molecular biology have shifted epilepsy research from a focus on phenotypic characteristics to genetic underpinnings. To date, numerous genes and candidate genes associated with epilepsy have been identified. The condition may arise from a primary genetic mutation or as a secondary consequence of identifiable structural abnormalities or metabolic disorders.[17] .Genealogical studies and genetic analyses have shown that epilepsy can be inherited through one or multiple genes, following dominant, recessive, or even combined inheritance patterns. As a result, both

inherent genetic predispositions and acquired environmental influences contribute to the onset and progression of epilepsy.

Diagnostic criteria

The primary tool for evaluating a patient with epilepsy is electroencephalography (EEG). When abnormalities are detected, EEG can aid in classifying seizures as either focal or generalized, and it can also help identify the patient's specific epileptic syndrome. In most cases, it provides valuable insights into seizure prognosis and can guide more effective treatment strategies.[18].When neuroimaging appears normal and surgery is being considered, video-EEG monitoring becomes an essential tool for identifying the type of seizure and locating the brain's epileptogenic zone.[19]. In emergency situations, computed tomography (CT) scans can be useful, though localized lesions are identified in only about 30% of patients.[20] .When using magnetic resonance imaging (MRI) to evaluate focal epilepsy, specific protocols should be followed based on the seizure onset location identified through clinical and EEG findings The primary objective of an MRI investigation in epilepsy is to identify its underlying cause.[21]. Pre surgical examination also provided here.Both MRI epilepsy techniques and post-processing reconstructions should be considered, as they help identify and manage specific types of primary focal epilepsies effectively.Fig.2([22]

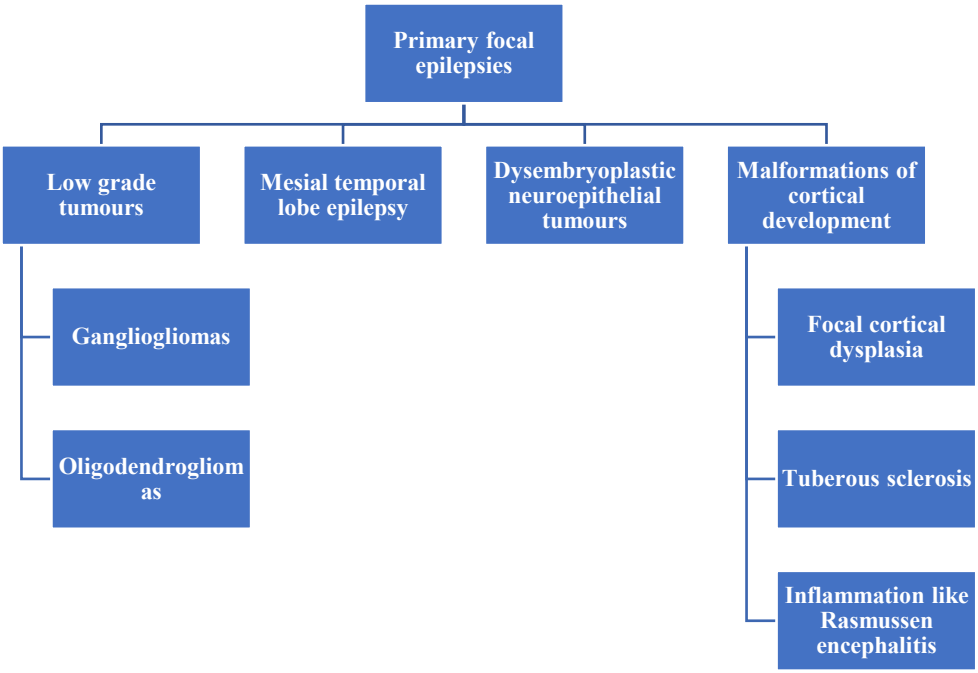


Fig.2.Types of Primary Focal Epilepsies

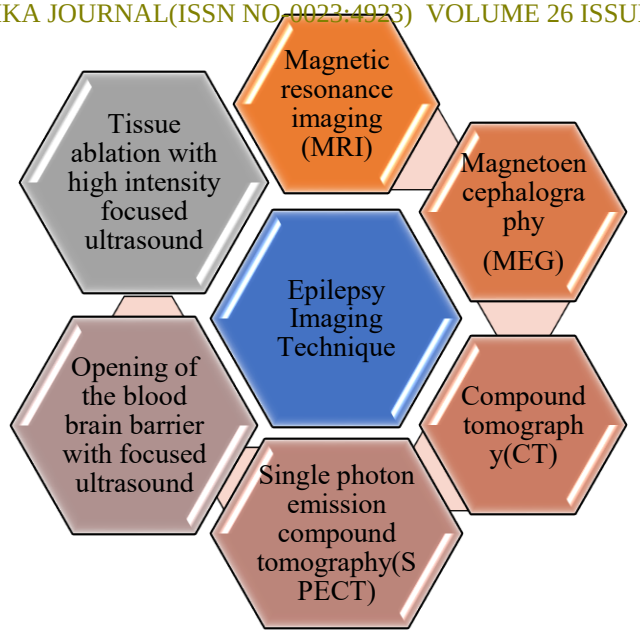


Fig.3.Types of Functional Imaging Methods Used to Detect the Epilepsy. [23], [24].

Causes:

The exact cause of epilepsy remains largely unknown. The term "epilepsy" itself doesn't indicate the source or severity of an individual's seizures. While some cases are linked to genetic factors, epilepsy can also be triggered by head injuries, strokes, infections, high fevers, or tumours. Although it can affect people of all ages, genetics appear to play a particularly important role in cases involving very young children. For example, while a serious head injury is a known risk factor for seizures, not everyone who experiences such trauma will go on to develop epilepsy.[25]. Patients with epilepsy report that certain types of the condition, known as reflex epilepsies, require specific triggers—such as reading or flashing lights—for seizures to occur. Other commonly reported triggers include emotional stress, lack of sleep, heat exposure, alcohol consumption, and fever. Importantly, the impact of these triggers can vary from person to person. In women, hormonal fluctuations related to the menstrual cycle can influence seizure patterns, sometimes leading to a form known as catamenial epilepsy, where seizures are linked to the menstrual cycle. ([26].

In the neonatal period and early infancy, the most common causes of hypoxic-ischemic encephalopathy include central nervous system (CNS) infections, trauma, congenital abnormalities of the CNS, and metabolic disorders. In late infancy and early childhood, febrile seizures are often triggered by CNS infections and trauma. Well-defined epilepsy syndromes are typically observed in children. During adolescence and adulthood, seizures are more likely to result from secondary causes related to CNS damage. In older adults, cerebrovascular disease is the leading cause of dementia, though other causes include CNS tumours, head injuries, and various degenerative conditions.[27]. Fig.4.

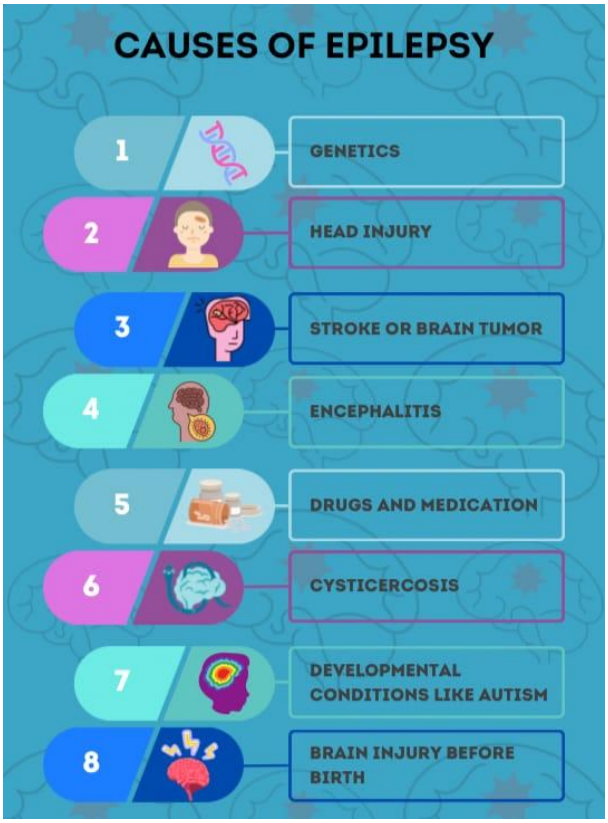


Fig .4 Most common causes of epilepsy

Signs and Symptoms

From a neurological perspective, epilepsy is marked by abnormal brain activity that leads to seizures, often resulting in a loss of consciousness, unusual behaviour, or emotional disturbances. A diagnosis is typically made when a person experiences at least two unprovoked Epilepsy—not caused by identifiable conditions like opioid withdrawal or severe Hypoglycaemia. Seizures usually originate in a specific brain region, disrupting the functions controlled by that area. Since the brain's left hemisphere governs the right side of the body, and vice versa, the location of the seizure's origin affects symptoms accordingly. Physicians usually classify seizures as either generalized or focal based on where and how the abnormal activity begins.[28]. Epilepsy symptoms and signs may include brief episodes of confusion, fixed staring spells, sudden body stiffness, uncontrollable jerking movements, loss of awareness or responsiveness, and emotional signs such as anxiety or fear.[29].

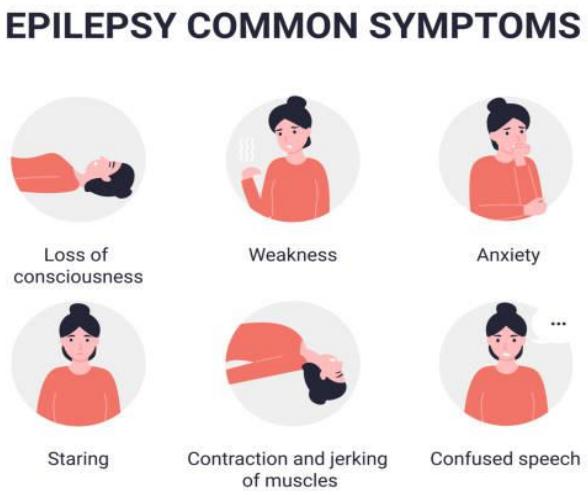


Fig.5 Common symptoms of Epilepsy

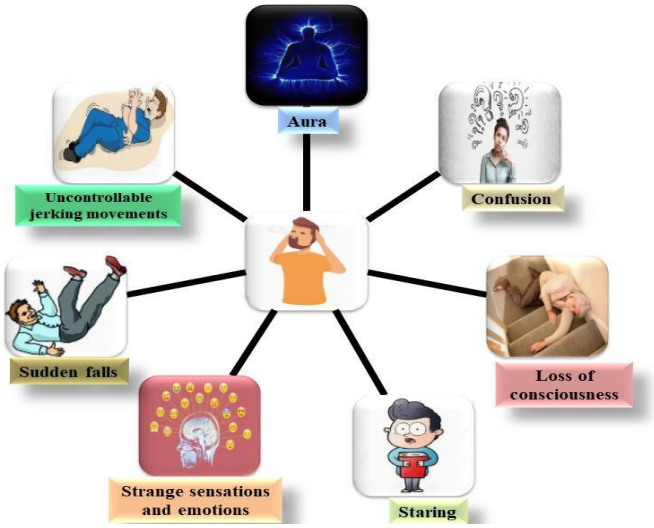


Fig .6 Some More Symptoms of Epilepsy [30].

Management

The terms antiepileptic and anticonvulsant are often used interchangeably. An anticonvulsant refers to a substance that prevents seizures in laboratory animals during experimental studies,

while an antiepileptic drug is one prescribed to manage and treat the 32 recognized types of epilepsy in humans.[31].

Management Principles

Any underlying causes or triggers of epilepsy—such as cerebral tumours—must be identified and treated. Patients should be educated about the nature of the disease, the expected duration of treatment, and the importance of strict adherence to their medication regimen. They should also be made aware of lifestyle factors that may trigger seizures, including alcohol consumption and sleep deprivation. Additionally, considerations should be given to the patient's development and learning needs. Therapeutic strategies may involve inhibiting T-type calcium channels and targeting excitatory neurotransmitters like glutamate. [32].

Medical Treatment

The most commonly used treatment for most patients with epilepsy is antiepileptic drug (AED) therapy, which aims to achieve four key goals: preventing seizures or minimizing their frequency, avoiding the long-term side effects of treatment, supporting patients in maintaining or returning to their usual social and work-related activities, and helping them lead a normal life. The decision to initiate AED therapy should be guided by a comprehensive assessment of the risk of seizure recurrence, the potential impact of continued seizures on the patient, and the pros and cons of the specific medication being considered. [33]. Whether to initiate treatment after a single seizure remains a topic of debate. However, if there is clear evidence that the seizure was caused by an identifiable lesion—such as a CNS tumour, infection, or trauma—and that lesion is known to be epileptogenic, then treatment is warranted. The primary aim of AED therapy is the complete elimination of seizures. The likelihood of epilepsy recurrence varies depending on the type and range of seizures. Patients with congenital neurological abnormalities or epileptiform activity on EEG are at particularly high risk of recurrence, with rates approaching 90%. When considering AED treatment, the views and preferences of the patient and their family should be taken into account. In some cases, early initiation of AEDs may be beneficial to prevent future epilepsy. The possibility of future seizures can be particularly distressing for individuals who need to drive, maintain employment, or care for family members. The risk of seizure recurrence varies depending on the specific type of epilepsy and any associated neurological or medical conditions. However, starting pharmacological treatment carries its own risks, with side effects occurring in

approximately 30% of patients after initial therapy. In children, long-term use of these medications presents additional challenges, particularly concerning brain development,

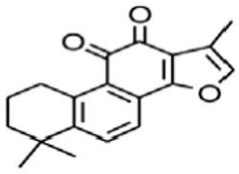
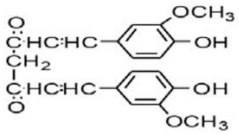
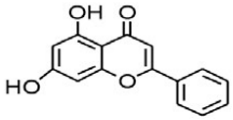
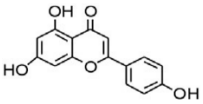
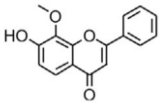
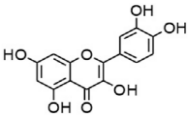
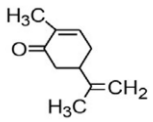
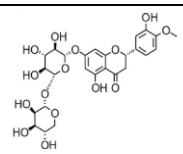
learning, and behaviour.[34],[35]

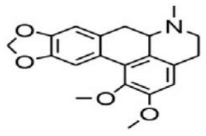
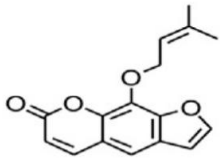
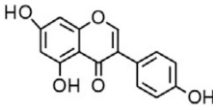
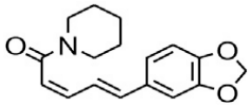
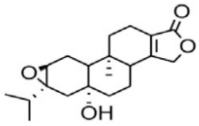
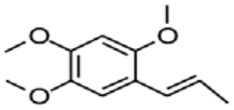
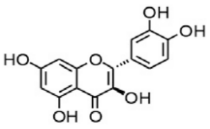
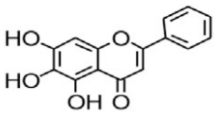
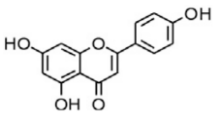
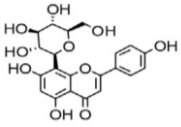
The selection of an antiepileptic drug (AED) or drug combination that effectively controls seizures with manageable side effects should be made by the treating physician or healthcare provider. It is widely accepted that up to 50% of patients can achieve complete seizure control, while an additional 25% may see substantial improvement. Treatment outcomes depend on factors such as seizure type, family history, and the severity of underlying neurological issues, with higher success rates seen in individuals with newly diagnosed epilepsy. When considering whether to initiate AED therapy, factors such as the risk of seizure recurrence, the impact of continued seizures, and the potential benefits and drawbacks of the medication in preventing further episodes should all be evaluated. Patients with congenital neurological abnormalities or epileptiform activity on an EEG face a high risk of seizure recurrence—up to 90%. Furthermore, individuals with brain lesions, a history of symptomatic epilepsy, or Todd's paralysis (a temporary paralysis following a seizure) are also more likely to experience recurrent epilepsy.[36], [37]

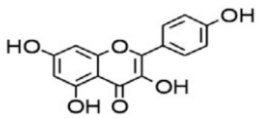
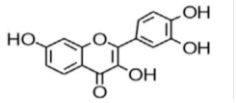
Surgical management

When epilepsy significantly disrupt quality of life and cannot be controlled despite optimal medical treatment, surgical intervention should be considered. However, assessing these impacts can be difficult, as intractable epilepsy encompasses more than just frequent seizures. While some individuals with drug-resistant epilepsy experience only mild impairment, others may be deeply affected by even infrequent episodes. Some patients have undergone surgery and achieved complete epilepsy freedom, yet remain unable to work due to lasting impairments. If epilepsy persist after two high-dose monotherapy trials with appropriate AEDs and one trial of combination therapy, surgery becomes a potential option—especially when a surgically treatable brain abnormality is identified as the source. [38],[39]

Natural compounds used to treat epilepsy

Natural drugs	Compounds	Chemical Structure	Reference
Salvia miltiorrhiza Bunge	Tanshinone IIA [40]		(Buenafe, O.E Et al 2013)
Curcuma longa L.	Curcumin [41]		(Kiasalari, Z.,Et al 2013)
Passiflora coerulea L. var. Hort.	Chrysin [42]		(Xiang, C.,Et al 2014)
Matricaria chamomilla L.	Apigenin [42]		(Xiang, C.,Et al 2014)
Scutellaria baicalensis Georgi	Wogonin [43]		(Tan, X. Q.,Et al 2014)
Bupleurum chinense	Quercetin [42]		(Xiang, C.,Et al 2014)
Herba Menthae Haplocalycis	Carvone [42]		(Xiang, C.,Et al 2014)
Crataegus pinnatifida Bunge	Hesperidin [42]		(Xiang, C.,Et al 2014)

Platycodongrandiflorus	Nantenine [43]		(Tan, X. Q.,Et al 2014)
Cnidium monnier (L.) Cuss	Osthole [42]		(Xiang, C.,Et al 2014)
Soybean (Glycine max (L.)	Genistein [43]		(Tan, X. Q.,Et al 2014)
Piper nigrum L.(pepper berries)	Piperine [43]		(Tan, X. Q.,Et al 2014)
Tripterygium wilfordii Hook F	Triptoli [44]		(Sun, Z., Du, M.,Et al 2018)
Acorus tatarinowii Schott	α-asarone [45]		(Yuan, X.,Et al 2019)
Green tea	Catechin [46]		(Ahmad, N.,Et al 2020)
Astragalus spp.	Baicalin [43]		(Tan, X. Q.,Et al 2014)
Citrus aurantium L	Naringin [43]		(Tan, X. Q.,Et al 2014)
Folium Sennae	Vitexin [43]		(Tan, X. Q.,Et al 2014)

Achillea millefolium L.	Kaempferol [43]		(Tan, X. Q.,Et al 2014)
Smoke tree (Cotinus coggygria)	Fisetin [43]		(Tan, X. Q.,Et al 2014)

Tanshinone IIA:

Synonym: Dan Shen ketone

Biological source:Tanshinones were first isolated in 1934 from the intensely red rhizomes (roots) of S. Miltiorrhiza. [47]

Family: Lamiaceae

The lipophilic compound Tanshinone IIA (Tan IIA) is produced by the herb Salvia miltiorrhiza (Danshen), which is frequently utilised in Traditional Chinese Medicine. Its varied pharmacological qualities, including as anti-inflammatory, anti-cancer, neuroprotective, and anti-osteoporotic actions, have been uncovered by numerous studies. [48]. Anticonvulsant effects in seizure model. According to a critical assessment, TSIIA shows anticonvulsant properties in mouse and zebrafish seizure models. In zebrafish larvae exposed to pentylenetetrazol (PTZ), TSIIA decreased seizure activity and the production of c-fos, a sign of neuronal excitation. In mouse models, TSIIA showed biphasic anticonvulsant effects, with a hormetic response and maximum effectiveness at particular dosages. These results suggest that TSIIA may provide a new treatment option for seizures by adjusting neuronal excitability.[49]. The methods by which TSIIA affects synaptic plasticity in epileptic individuals have been determined by further research. When TSIIA was administered to hippocampal neurones exposed to magnesium-free circumstances, the production of synaptic proteins such postsynaptic density protein 95 and synaptophysin (SYN) as well as brain-derived neurotrophic factor (BDNF) increased. Remarkably, these effects were linked to the PI3K/Akt signalling pathway, which is necessary for synaptic function and plasticity. These results demonstrate how TSIIA may improve neuronal health and lessen synaptic damage in epileptic disorders. The methods by which TSIIA affects synaptic plasticity in epileptic individuals have been determined by further research[50]. Improvement of Cognitive Abilities, the frequency and severity of seizures were significantly reduced after TSIIA medication in a

rat model of lithium-pilocarpine-induced chronic epilepsy. Behaviour assessments conducted 53 days after treatment showed that TSIIA improved cognitive function, as demonstrated by decreased seizure activity and better performance on learning and memory tests. The benefits were dose-dependent and more noticeable at higher dosages [51].

Curcumin:

Synonym: Turmeric, Saffron India, Curcuma

Biological source: It is derived from the rhizome of the turmeric plant, Curcuma longa.

Family: Zinger family (Zingiberaceae)

Turmeric (Curcuma longa), a plant belonging to the ginger family (Zingiberaceae), originated in India and is now cultivated in various regions around the world, including Southeast Asia, China, and Latin America.[52],[53] .Turmeric is a widely used spice in India and other Asian countries, valued for its distinctive flavour and vibrant colour in curry preparation.[54] ,[55] .India is the largest producer and leading exporter of turmeric. According to reports, the global turmeric market was estimated at approximately 1.7 million metric tons and is projected to grow substantially by 2027. ([56,57] In 2016, the global curcumin market was valued at approximately half a billion US dollars and is expected to grow at a compound annual growth rate (CAGR) of 13% between 2018 and 2025. [56] Curcumin can interact with multiple biological targets and has demonstrated effectiveness against a range of diseases, such as cancer, cardiovascular conditions, neurological disorders, and autoimmune diseases. [58],[59].Turmeric's main ingredient, curcumin, has demonstrated promise as an additional epilepsy treatment. According to a study, curcumin's anti-inflammatory, antioxidant, and neuroprotective qualities may be the reason for its effectiveness in treating seizures.[60].In an epileptic rat model, curcumin decreased neuronal mortality and suppressed NLRP3 inflammasome activation, according to a study published in Current Neurovascular Research. This implies that curcumin might be used to treat epilepsy because of its neuroprotective qualities.[61].An investigation that was published in the Egyptian Journal of Basic and Applied Sciences emphasised the neuroprotective qualities of curcumin. Through avoiding apoptosis and changing the Wnt/β-catenin and autophagy pathways, the study discovered that it decreased PTZ-induced epilepsy.[62]. Despite these encouraging results, curcumin's limited medicinal uses are caused by its low bioavailability. Researchers are looking into new drug delivery methods, like nanocarriers, to increase curcumin's ability to cure epilepsy.[63].

Preclinical research suggests that curcumin may be used to treat epilepsy; however, additional clinical trials are required to confirm its safety and effectiveness in people.

Chrysin:

Synonym: Chrysine, Flavone X

Biological source: It is a natural flavonoid, and is found in various biological sources, including honey, propolis, and blue passion flowers (Passiflora caerulea and Passiflora incarnate). It's also found in other plants and even some mushrooms.

Family: Flavone family

Chrysin, a naturally occurring flavonoid present in passionflower and honey, has been the subject of epilepsy study because of its possible neuroprotective and anticonvulsant qualities. In 2023, a chrysin-loaded nanoemulsion (CH NE) was created to cure rats suffering from status epilepticus brought on by lithium/pilocarpine. According to the formulation, the intensity of the seizures decreased. Oxidative stress indicators and neurotransmitter balance have returned. lowering the polarisation of pro-inflammatory (M1) and anti-inflammatory (M2) microglia AMPK/SIRT-1/PGC-1α pathway regulation to restore energy metabolism Surprisingly, the nanoemulsion improved the delivery of chrysin to the brain in comparison to conventional suspensions.[64]. Chrysin-Loaded PLGA Nanoparticles in Kindling-Induced Epilepsy: In a different study, rats' Pentylenetetrazole (PTZ)-induced kindling was treated with chrysin encapsulated in poly(lactic-co-glycolic acid) nanoparticles. Activation of the Nrf2/ARE/HO-1 pathway, enhanced antioxidant defences, and a reduction in neuronal apoptosis and oxidative stress were among the results. These findings suggest that chrysin may help reduce the oxidative damage linked to epileptic episodes.[65]. Research Using epilepsy to Examine Chrysin Isolated from Pyrus Pashia Fruits: Rats with maximum electroshock (MES) and PTZ-induced seizures demonstrated notable anticonvulsant action when chyrsin was isolated from Pyrus pashia fruits. At doses ranging from 2.5 to 10 mg/kg, chyrsin's ability to shorten seizure duration and delay onset demonstrated its antiseizure potential.[66]. A study of a number of extracts from Passiflora incarnata revealed that although the methanolic extract had a higher chrysin content, it lacked the anticonvulsant qualities of the aqueous and hydroethanolic extracts. Furthermore, there were no discernible anticonvulsant effects from isolated chrysin at 1 mg/kg. This implies that P. incarnata's anticonvulsant qualities might be more significantly influenced by other ingredients.[67]. Anti-

inflammatory Effects: By controlling microglial activation, chyrsin may lessen neuroinflammation linked to epilepsy, shifting the scales in favour of anti-inflammatory therapies.[68].

Apigenin:

Synonym: Apigenine, Chamomile

Biological source: It is found in many plants, particularly in vegetables and fruits like parsley, celery, and chamomile, as well as in herbs, spices, honey, and plant-based beverages like tea, beer, and wine.

Family: Apiaceae

Celery, parsley, and chamomile are natural sources of apigenin, a flavonoid that has been studied for possible neuroprotective and anticonvulsant effects in epilepsy. Benefits for cognition and neuroprotection in temporal lobe epilepsy. Anticonvulsant Action: Oral administration of 50 mg/kg apigenin for six days considerably postponed the onset of seizures and lessened their intensity.[69].

Cognitive Improvement: Treated rats showed greater memory and spatial learning in the Y-maze and Morris water maze tests.[70]. Apigenin increased the number of viable neurones in the hippocampus hilus region while decreasing the release of cytochrome C, indicating that the mitochondrial apoptotic pathway is inhibited.[71] .These results suggest that the neuroprotective and anticonvulsant properties of apigenin facilitate memory restoration.[72] .Lowering oxidative stress and preventing ferroptosis Reduction of Oxidative Stress: Apigenin reduced oxidative damage caused by myeloperoxidase in the brain tissue of epileptics. PNAS Ferroptosis Inhibition: By preventing ferroptosis, a kind of dementia-related programmed cell death, the medication provided neuroprotection. These results imply that apigenin can lessen oxidative damage and neuronal death in epilepsy.[73].Properties of anticonvulsants: Delays the onset of seizures and lessens their intensity. Using anti-apoptotic mechanisms to stop hippocampus neurones from dying is known as neuroprotection. Cognitive Support: Improves memory and learning processes that epilepsy impairs. lowers reactive oxygen radicals and lipid peroxidation, which lessens oxidative stress. Iron-dependent cell death processes linked to epilepsy are inhibited by ferroptosis.

Wogonin:

Synonym: 5,7-Dihydroxy 8-methoxyflavone

Biological source: It is a natural flavonoid, primarily isolated from the dried roots of the traditional Chinese herb Scutellaria baicalensis. It's also found in other plants like Oroxylum indicum.

Family: Flavone subclass of Flavonoids

The neuroprotective and anticonvulsant qualities of wogonin, a flavonoid produced from Scutellaria baicalensis, have been thoroughly investigated in epileptic models. Below are the main study findings together with the appropriate sources.[74] In patients with temporal lobe epilepsy (TLE), wogonin exhibits neuroprotective benefits that dramatically lower seizure frequency and intensity. It reduced oxidative stress indicators including malondialdehyde (MDA) and raised glutathione (GSH) levels. Less hippocampal neuronal death was shown via a histological analysis. Wogonin had an impact on the expression of genes linked to oxidative stress (Nrf2, HO-1), inflammation (IL-1β, TNF-α, NF-κB), and apoptosis (Bcl-2, Bax, caspase-3).[75]. GABA-A Receptor-Mediated Action Mechanism: By functioning as a partial agonist at the benzodiazepine site of GABA_A receptors, wogonin helps to avoid seizures. The inhibition of chloride influx brought on by the GABA_A receptor antagonist flumazenil confirmed wogonin's action on these receptors.[76] Broad Neuroprotective Benefits in CNS disorders: A 2024 review emphasised wogonin's neuroprotective qualities in a range of disorders affecting the central nervous system, such as epilepsy. Wogonin regulates important signalling pathways like ROS, NF-κB, and MAPK, which gives it anti-inflammatory, antioxidant, and antiapoptotic qualities. Its possible therapeutic effects in treating epilepsy and other neurological diseases are supported by these processes [76].

Wogonin's Antiepileptic Mechanisms:

Antioxidant Activity: Reduces oxidative stress by altering the Nrf2 and HO-1 pathways. Anti-inflammatory effects: Pro-inflammatory cytokines such as TNF-α and IL-1β are decreased when NF-κB is inhibited. Inhibiting caspase-3 activation and balancing pro- and anti-apoptotic proteins (Bax, Bcl-2) are examples of anti-apoptotic characteristics. GABAergic Modulation: By partially activating GABA_A receptors, this mechanism raises inhibitory neurotransmission.

Quercetin:

Synonym: Pentahydroxyflavone, Quercetine

Biological source: It found mostly in onions, grapes, berries, cherries, broccoli, and citrus fruits.

Numerous studies have examined quercetin, a naturally occurring flavonoid present in a variety of fruits and vegetables, for its possible neuroprotective and anticonvulsant properties in epilepsy. neuroprotective effect through ferroptosis suppression.By blocking ferroptosis through the SIRT1/Nrf2 pathway, quercetin reduces kainic acid-induced epileptic episodes. The results showed that quercetin restored redox balance and neuronal integrity in mice, hence lowering seizure severity and neuronal death.[77]. Modulation of microglia and anti-inflammatory Through the inhibition of NF-κB activation and the reduction of TNF-α and IL-1β levels, quercetin decreased neuroinflammation in glial cells during epileptic episodes. The quantity and severity of seizures consequently declined.[78]. Quercetin demonstrated potent antioxidative neuroprotection in PTZ-induced seizure models by raising the threshold for seizures, lowering lipid peroxidation, and boosting antioxidant capacity.[79]. Changes to the GABAergic System.By affecting the expression of the GABA_A receptor subunit, quercetin may have changed inhibitory neurotransmission. Exposure to kainic acid decreased the hippocampal levels of GABA_A α5 subunits.[80]. Enhancements in bioavailability and delivery. Nanoformulations like quercetin-loaded nanoparticles have been researched to boost quercetin's therapeutic efficacy in seizure models due to its low bioavailability.[81]. Ferroptosis Pathway Inhibition: Quercetin increased the Nrf2 signalling pathway, which inhibits ferroptosis and lowers oxidative stress. As a result, mice experienced less seizures brought on by kainic acid.[82].Anti-inflammatory and neuroprotective qualities Quercetin reduces neuroinflammation and the severity of seizures in mice by inhibiting TNF-α, IL-1β, and NF-κB in glial cells[83] .An increase in antioxidant activity and seizure threshold. In PTZ-induced animals, quercetin enhanced antioxidant defences, reduced markers such as MDA and iNOS, and increased seizure threshold.[84].

Carvone:

Synonym: Carvol

Biological source: It is naturally produced by various plants, particularly those in the genera Mentha, Carum, and Anethum. It is a key component of the essential oils found in plants like spearmint (Mentha spicata), caraway (Carum carvi), and dill (Anethum graveolens).

Family: Terpenoid family

In numerous animal models of epilepsy, carvone, a monoterpene present in essential oils like those made from caraway seeds (Carum carvi), has been studied for possible anticonvulsant effects. [85]. Cyano-Carvone in Pilocarpine-Induced epilepsy: A study that was published in Cellular and Molecular Neurobiology examined how cyano-carvone, a derivative of carvone, affected mice who had seizures brought on by pilocarpine. By postponing the start of seizures and lowering fatality rates, the substance showed dose-dependent anticonvulsant efficacy. Additionally, cyano-carvone had antioxidant properties and increased acetylcholinesterase activity, suggesting a neuroprotective impact, via decreasing lipid peroxidation and nitrite production in the hippocampus.[86] .Alpha, Beta-Epoxy-Carvone in Various epilepsy Models: In a study published in Neuroscience Letters, alpha,beta-epoxy-carvone (EC), another carvone derivative, was examined using a variety of seizure models, such as those brought on by picrotoxin, maximum electroshock (MES), and pentylenetetrazole (PTZ). Significant anticonvulsant effects were demonstrated by EC, which increased seizure latency and prevented convulsions. The results indicate that EC may work via blocking voltage-gated sodium channels rather than controlling GABA_A receptors. [87]. A comparative analysis of the anticonvulsant properties of various epoxycarvone stereoisomers was reported in Molecules. All isomers increased seizure latency in PTZ-induced animals, however some, like (+)-cis-EC and (+)-trans-EC, had a more pronounced effect. These findings imply that the stereochemistry of carvone derivatives influences their anticonvulsant properties. [88]. (S)- (+)-carvone dramatically increased convulsion latency in animal models of PTZ and picrotoxin-induced seizures, but R- (−)-carvone exhibited no such effects. This implies that the anticonvulsant effects of carvone are stereoselective.[89]. An article about the anticonvulsant qualities of caraway seed essential oil and aqueous extract—both of which are rich in carvone—was published in the Iranian Journal of Medical Sciences. Both formulations shortened the time until seizures started in mice with PTZ-induced seizure

models, but the essential oil worked better.[90].The results support the traditional use of caraway in the treatment of seizures and point to carvone as a possible active ingredient.[91]. These results suggest that carvone and its derivatives may influence oxidative stress pathways, neurotransmitter systems, and ion channel activity to produce anticonvulsant effects. To completely comprehend their therapeutic potential and safety in people, more investigation is required, including clinical trials.

Hesperidin:

Synonym: Cirantin , Hesperidoside

Biological source: It a bioflavonoid, is primarily found in citrus fruits like oranges, lemons, and grapefruits. It's particularly abundant in the peel and membranous parts of these fruits. Hesperidin is also found in other plants, though citrus fruits are the main source.

Family: Rutaceae

Hesperidin, a flavonoid mostly present in citrus fruits, has drawn attention in epilepsy research because of its possible anticonvulsant and neuroprotective qualities. [92]. Mice were given 100 and 200 mg/kg of hesperidin orally for seven days prior to pentylenetetrazole (PTZ) inducing convulsions. The increased dosage (200 mg/kg) markedly postponed the onset of convulsions while reducing oxidative stress markers such as lipid peroxidation and nitrite levels. Additionally, it restored the antioxidant enzymes catalase, glutathione, and superoxide dismutase, as well as the mitochondrial complex I, II, and IV. Remarkably, when combined with a lower dose of hesperidin (100 mg/kg), subtherapeutic doses of gabapentin or diazepam increased their neuroprotective effects, demonstrating a synergistic interaction at the GABA_A/benzodiazepine receptors.[93].

Hesperidin pretreatment decreased PTZ-induced hyperactivity and enhanced seizure latency, according to studies using zebrafish models. Hesperidin lowers inflammation and neuronal hyperexcitability via modifying the CREB-BDNF signalling pathway, lowering interleukin-10 levels, and lowering the expression of c-fos, a neuronal excitation marker, according to molecular research.[94]. Hesperidin had no discernible impact on the onset of seizures, but it successfully avoided PTZ-induced memory consolidation failures in adult zebrafish, suggesting that it might be able to preserve cognitive abilities linked to epilepsy.[95]. A mouse model of temporal lobe epilepsy caused by kainic acid was used to evaluate hesperetin, an

aglycone derivative of hesperidin. According to the study, oral hesperetin administration decreased hippocampal granule cell dispersion, postponed the onset of seizures, and inhibited the expression of pro-inflammatory chemicals generated by activated microglia. These results imply that hesperetin may have neuroprotective qualities in cases of temporal lobe epilepsy. [96].Together, these results show that hesperidin has a variety of uses in the treatment of epilepsy, including lowering oxidative stress, seizures, neuroinflammation, and cognitive impairment. More clinical studies are required to prove hesperidin's safety and effectiveness in treating epilepsy in humans, even with encouraging preclinical results.

Nantenine:

Synonym: Domestine. Nantenin.

Biological source: It is an alkaloid found in the plant Nandina domestica as well as some Corydalis species.

Family: Berberidaceae.

The possible anticonvulsant properties of nantenine, an aporphine alkaloid derived from plants like Nandina domestica, have been the subject of epilepsy study.[97]. Anticonvulsant activity: In animal models of epilepsy, nantenine has demonstrated potential. It has been specifically tested on male albino mice that have been given pentylenetetrazole (PTZ) and maximum electroshock (MES), both of which cause seizures. The drug was given intraperitoneally in doses ranging from 20 to 50 mg/kg. Studies have shown that nantenine has anticonvulsant qualities because it increases seizure latency while decreasing epilepsy intensity.[98]. It is believed that nantenine's anticonvulsant properties are related to its capacity to influence calcium-mediated signalling pathways. By decreasing calcium input to neurones, nantenine may lessen neuronal hyperexcitability, a defining feature of epileptic seizures. A pivotal study investigated nantenine's effects on seizures induced by pentylenetetrazole (PTZ) and maximal electroshock (MES) in mice. At lower doses (20–50 mg/kg, intraperitoneally), nantenine significantly inhibited both PTZ- and MES-induced seizures, suggesting its potential as an anticonvulsant agent. However, at higher doses (≥75 mg/kg, intraperitoneally), nantenine exhibited convulsant activity. This biphasic effect may be related to its modulation of Na^+, K^+-ATPase activity, where low doses stimulate the enzyme, leading to decreased intracellular calcium influx, while high doses inhibit the enzyme, resulting in increased calcium influx and potential excitotoxicity. These results are promising, but it's crucial to remember that nantenine's biphasic effects require precise

dosage calculations. The safety and effectiveness of nantenine in treating human epilepsy have not yet been investigated through clinical trials. To determine suitable dosage schedules and the therapeutic potential, more research is required.

Osthole:

Synonym: Coumarin

Biological source: It is a coumarin derivative found in several medicinal plants such as Cnidium monnieri and Angelica pubescens

Family: Umbelliferae

Oshole, a naturally occurring coumarin derivative present in plants like Cnidium monnieri, has drawn attention in epilepsy research because of its possible anticonvulsant qualities. [99]. Anticonvulsant Effects in Animal Models: Using the maximal electroshock seizure (MES) paradigm, Osthole significantly reduced seizures in mice Luszczki Et al 2009 A dose-dependent reduction in seizure activity was shown by the effective dose (ED_{50}), which varied between 259 and 631 mg/kg. The researchers came to the conclusion that osthole was a viable option for future advancement as a state-of-the-art epilepsy treatment.[100].Mechanistic Knowledge: Regulating Microglial Activity Studies have demonstrated that Osthole alters the Notch signalling pathway to prevent the growth of BV-2 microglial cells stimulated by kainic acid. Pro-inflammatory cytokines such as TNF-α and IL-6 are decreased by this regulation, which may offer protection against epilepsy and other neurodegenerative diseases marked by microglial activation.[101]. Connection to conventional antiepileptic drugs more research has been done on the relationship between osthole and common antiepileptic drugs. Osthole enhanced mice's defences against seizures brought on by MES when used in conjunction with carbamazepine or phenobarbital. Thus, osthole may have synergistic benefits when combined with traditional therapies. Even while these results are promising, it's crucial to remember that the great majority of research has been done using animal models. The safety and effectiveness of osthole in people with epilepsy require further investigation, including clinical trials.[102].

Genistein:

Synonyms: Genisteol,Sophoricol.

Biological source: It is primarily found in soy-based foods and products. Other legumes, like chickpeas, also contain small amounts. Additionally, some other plant foods like broccoli, cauliflower

Family: Isoflavone family

Studies on epilepsy have examined the possible neuroprotective and anticonvulsant qualities of genistein, a naturally occurring isoflavone present in soy products. According to research, genistein may have an impact on several pathways linked to seizure activity and the resulting neuronal damage.[103]. Neuroprotective effects through the JAK2/STAT3 and Keap1/Nrf2 pathways. In a study by Li et al. (2021), genistein was given to developing rats that had epilepsy caused by pentylenetetrazole (PTZ). Less severe seizures and a longer seizure latency were the outcomes of the drug. In the hippocampus, genistein reduced neuronal loss and astrocyte and microglia activation by inhibiting JAK2/STAT3 inflammatory signalling and activating the Keap1/Nrf2 antioxidant pathway. These results suggest that genistein may have neuroprotective effects by reducing oxidative stress and inflammation linked to epilepsy.[104]. Preventing Seizures-Related Respiratory Arrests (S-IRA) : The impact of genistein on seizure-induced respiratory arrest (S-IRA) in DBA/1 mice, a model of sudden unexpected death in epilepsy (SUDEP), was examined by Guo et al. in 2021. Without changing the severity of seizures, genistein treatment dramatically decreased the incidence of S-IRA. Since α1 or serotonin receptor antagonists did not reverse the protective effect, it was determined that α2 adrenoceptor activation was responsible for it. By focussing on particular adrenergic pathways, genistein may be able to prevent SUDEP, according to this study.[105]. Reducing cognitive dysfunction and synaptic impairment In a cognitive investigation, ovariectomised rats with kainic acid-induced convulsions showed decreased hippocampus synaptic plasticity along with memory and spatial learning deficits. Prior to treatment, a low dose of genistein (0.5 mg/kg) reduced the cognitive deficits and synaptic dysfunctions. Genenistein has a dosage-dependent effect on cognitive functioning after a seizure, as evidenced by the lack of advantages from a larger dose (5 mg/kg).[106]. There are links to oestrogenic and serotonin pathways. In ovariectomised mice with PTZ-induced convulsions, Asadi-Shekaari et al. (2017) investigated the anticonvulsant effects of genistein. The effect of genistein's elevation in seizure threshold was lessened by antagonists of 5-HT3 serotonin and oestrogen receptors. This shows that genistein may be able to modulate neurotransmitter

systems linked to seizure activity, and it implies that oestrogenic and serotonergic pathways may be involved in its anticonvulsant actions.These studies all demonstrate the various ways that genistein controls brain damage and seizure activity through neurotransmitter-mediated, antioxidant, and anti-inflammatory pathways.Despite these encouraging results, more clinical studies are required to ascertain the safety and effectiveness of genistein in epileptic patient groups.

Piperine:

Synonym: Piper Nigrum,

Biological source: Piperine is found in black pepper (piper nigrum), white pepper, and long pepper (piper longum)

Family : Piperaceae.

Because of its anticonvulsant qualities, piperine, the primary ingredient in black pepper, has showed promise in studies on epilepsy. Numerous investigations have looked into its workings and its medical uses.Transient receptor potential vanilloid type 1 (TRPV1) agonists, such as piperine, have been found to activate the TRPV1 receptor. It considerably decreased the intensity of seizures and postponed their onset in animal studies. The TRPV1 receptor is involved in piperine's anticonvulsant function, as evidenced by the fact that the TRPV1 antagonist capsazepine reversed these effects.[107].

Neuroprotection and Inflammation Modulation: Treatment with piperine decreased the frequency and intensity of seizures in models of pilocarpine-induced epilepsy. Additionally, it reduced levels of oxidative stress and inflammatory markers and improved memory impairment. Furthermore, piperine controlled apoptotic proteins, indicating that it may be able to shield neurons from harm brought on by seizures.Anti-inflammatory and neuroprotective effects Piperine decreased seizure frequency and intensity in a model of epilepsy generated by pilocarpine. Additionally, it enhanced cognitive performance and reduced inflammation and oxidative stress.[108]. Monoamine Modulation: By raising serotonin levels, piperine may reduce depression frequently linked to epilepsy. Its antidepressant benefits in epilepsy may be attributed to its function as a monoamine oxidase (MAO) inhibitor.[109]. Enhanced Drug Bioavailability: Formulating piperine into nanoparticles has been found to improve its oral bioavailability and brain penetration. In rats, piperine-loaded nanoparticles exhibited enhanced dissolution rates and significantly higher brain

concentrations compared to unformulated piperine, suggesting potential for improved therapeutic efficacy in epilepsy treatment.[110].

α-asarone:

Synonym:Asarone, isoasaron, and asarum camphor.

Biological source: It is found in the roots of the asarabacca plant (Asarum europaeum L) and (the calamus plant (Acorus calamus L) It is also present in in the Elemuy tree

Family: Phenylpropanoid

Numerous preclinical investigations have demonstrated the prospective antiepileptic benefits of α-Asarone, a bioactive chemical produced from Acorus gramineus. Studies suggest that α-asarone may have anticonvulsant effects via a variety of channels, including as reducing neuroinflammatory pathways and modifying GABAergic neurotransmission.Enhancement of GABAergic Inhibition: Studies have demonstrated that α-asarone improves tonic GABAergic inhibition in hippocampal neurons, hence lowering neural excitability. When GABA(A) receptor antagonists are administered, α-asarone-induced currents are suppressed, suggesting that GABA(A) receptor activation mediates this activity.In hippocampus neurons, α-asarone increases tonic GABAergic inhibition, which lowers neuronal excitability and seizure activity. Through GABA(A) receptors, it has been demonstrated to raise GABA-evoked currents.[111]. Neuroinflammation Reduction through the NF-κB Pathway: α-asarone pretreatment dramatically reduced proinflammatory cytokine levels and microglial activation in a rat model of pilocarpine-induced status epilepticus. This was linked to the suppression of the NF-κB signaling pathway, particularly by blocking IκB-α degradation and IKK-β activation, which in turn decreased NF-κB p65's nuclear translocation.Anti-inflammatory Action α-Asarone reduces pro-inflammatory cytokines, microglial activation in seizure models, and neuroinflammation in epilepsy via blocking the NF-κB pathway.[112] .Deense Against Brain Damage Caused by Seizures α-asarone decreased seizure severity and mortality and postponed seizure onset in rat models of pilocarpine-induced status epilepticus. Additionally, it protected the hippocampal neurons.[113].

Catechin:

Synonym: Catechu,polyphenol

Biological source: Catechins are found in a variety of plant-based food, with green tea and cocoa other sources include fruits like grapes,apples ,pears and cherries, red wine and various berries.

Family: Flavanoids

Preclinical research has looked into the possible antiepileptic benefits of catechins, especially epigallocatechin gallate (EGCG). These substances, which are prevalent in green tea, are well-known for their neuroprotective, anti-inflammatory, and antioxidant qualities.

Anticonvulsant Effects: One study evaluated how EGCG affected rats' kindling caused by pentylenetetrazole (PTZ). The findings showed that EGCG reduced oxidative stress brought on by PTZ kindling, improved cognitive impairment, and slowed kindling progression in a dose-dependent manner. Based on these findings, EGCG may be a promising treatment for epilepsy and a protective measure against seizure-induced cognitive impairment.[114]. Molecular Mechanisms: EGCG demonstrated anticonvulsant properties similar to those of levetiracetam, a common antiepileptic medication, in a rat model of chronic epilepsy brought on by PTZ. According to the study, EGCG has the ability to lower seizure activity via both molecular and inflammatory routes since it binds to synaptic vesicle protein 2A (SV2A), a target of many antiepileptic medications, and alters the expression of pro- and anti-inflammatory cytokines.[115].Neuroprotective Effects: Studies that used EGCG to biosynthesize selenium nanoparticles (EGCG-SeNPs) showed that these nanoparticles shielded mice against acute epileptic episodes brought on by PTZ. In addition to showing antioxidative, anti-inflammatory, and anti-apoptotic properties, the therapy decreased seizure length, latency, and severity. Furthermore, EGCG-SeNPs decreased neuronal death in hippocampus tissue and restored levels of inflammatory markers like TNF-α and IL-1β.[116].

Baicalin:

Synonym: Chinese skullcap, Huang Qin

Biological source: It is a flavone glycoside derived from the roots of a perennial herb Scutellaria baicalensis Georgi.[117] .

Family: Lamiaceae

The flavonoid molecule baicalin, produced by Scutellaria baicalensis, has drawn attention due to its possible anticonvulsant and neuroprotective properties in epilepsy. Numerous animal forms of epilepsy have been used to study its mechanisms and treatment advantages.[118]. Anticonvulsant and neuroprotective properties of pilocarpine in rats with epilepsy. Baicalin's effects on a pilocarpine-induced epileptic rat model were examined in a study that was published in Neurochemical Research. Baicalin significantly postponed the onset of seizures, decreased mortality, and decreased oxidative stress markers in the hippocampus, according to the study. Baicalin also decreased apoptosis and neuronal loss, suggesting that it may be used as an adjuvant for epilepsy.[119].Improvement of Neuroprotection and Cognitive Function via the TLR4/MYD88/Caspase-3 Pathway Baicalin's effects on neurodegeneration and cognitive dysfunction in rats with PTZ-induced epilepsy were examined in a study that was published in Drug Design, Development, and Therapy. The study found that baicalin triggered the TLR4/MYD88/Caspase-3 signaling pathway, which is linked to apoptosis and neuroinflammation, decreased hippocampal neurodegeneration, and enhanced cognitive performance.[120]. Autophagy activation and suppression of mitochondrial apoptosis. A PubMed study looked into how autophagy shields the hippocampus against pilocarpine and lithium chloride-induced status epilepticus. The results showed that baicalin activated autophagy, decreased indications of the mitochondrial apoptotic pathway, and increased autophagic markers to prevent apoptosis in hippocampus neurons.[121] Control of Bcl-2 and miR-497 in Kainic Acid-Induced Epilepsy Mice A study that was published in PMC examined how baicalin affected the expression of miR-497 and the regulation of Bcl-2 in a mouse model of kainic acid-induced epilepsy. The study found that baicalin boosted Bcl-2 and inhibited caspase-3 activation by lowering miR-497 expression. This decreased the death of hippocampal neurons and protected them.[122]

Vitexin:

Synonym: Orientoside

Biological source: It is found in a variety of plants, including passion flower, chaste tree, bamboo leaves, and hawthorn

Family: Senna

Impact of Anticonvulsants and Anxiolytics in Mouse Models In study published in Frontiers in Pharmacology, the effects of vitexin on mice with chemically induced seizures were examined. Higher doses of vitexin demonstrated dose-dependent protection against seizures brought on by GABA_A receptor antagonists like as picrotoxin and pentylenetetrazole (PTZ), offering up to 100% protection. It did not, however, offer any defense against seizures brought on by glutamate receptor agonists like kainic acid and NMDA. These results imply that the anticonvulsant effects of vitexin may be mediated by regulation of the GABAergic system.[123]. Impact of Neuroprotection on Hypoxic-Ischemic Brain Injury in Neonatals: An investigation into the effects of vitexin in a newborn rat model of hypoxic-ischemic brain injury—a condition that can result in epilepsy—was published in Molecular Neurobiology. Vitexin treatment decreased expression of the Na^+-K^+-Cl^− co-transporter 1 (NKCC1), decreased inflammation, enhanced blood-brain barrier integrity, and decreased seizure susceptibility. These findings suggest that vitexin may offer neuroprotection by reducing variables that contribute to epilepsy.[124]. PTZ-Induced Kindling's Long-Term Effects The long-term effects of vitexin were investigated in rats with epilepsy brought on by PTZ-induced kindling in a study that was published in Acta Neurobiologiae Experimentalis. When administered over an extended period of time, vitexin (2.5 mg/kg) decreased seizure severity without impairing liver or kidney function. This implies that vitexin may be a viable long-term treatment option for epilepsy. [125].

Kaempferol:

Synonym: Kaempherol,kempferol,Robigenin.

Biological source: It found in wide variety of plants, especially in fruits, vegetable, and some medicinal herbs. It is also found in tea and some spices

Family:Flavonol

The potential of kaempferol, a flavonoid present in many plants, as a therapy for epilepsy has been brought to light by recent studies. Research has shown that it has anticonvulsant benefits via a variety of pathways, including as antioxidant qualities, anti-inflammatory effects, and neurotransmitter system regulation.

The effects of kaempferol, quercetin, and catechin were assessed in a rat model of chronic epilepsy caused by pentylenetetrazole (PTZ) in both in vivo and in silico investigations on the condition that were reported in Metabolic Brain Disease. Kaempferol shown similar efficacy to the common antiepileptic medication levetiracetam, according to the data, which showed that these flavonoids considerably decreased seizure frequency, intensity, and length. Several antiepileptic medications target synaptic vesicle protein 2A (SV2A), which kaempferol binds to, according to molecular docking studies. This finding suggests a possible mechanism for kaempferol's anticonvulsant effects.Effects of Anticonvulsants in PTZ-Induced Seizures In a different study, kaempferol and other flavonoids were evaluated in mouse and zebrafish models of seizures caused by PTZ. Kaempferol alone had no anticonvulsant effect, although methylated naringenin compounds were more effective. These results, however, highlight how crucial structural alterations are to boosting flavonoids' therapeutic potential.[126]. GABAergic and glutamatergic pathways are involved in the mechanism;Another study found kaempferol in the medicinal plant Grewia tiliaefolia and demonstrated how it interacted with agonist (GABA_A) and antagonist (Glu-AMPA) receptors. These interactions imply that kaempferol may modulate excitatory and inhibitory neurotransmission to provide antiepileptic effects.[127].

Neuroprotection via Antioxidant and Anti-Inflammatory Properties Several models of CNS diseases, including epilepsy, have demonstrated the neuroprotective properties of kaempferol. It lowers oxidative stress and inhibits neuroinflammatory cytokines, such as TNF-α and IL-1β, which are increased in the brains of epileptics.[128].

Fisetin:

Synonym:Fiestin ,Fietin,cotinin

Biological source: It is founds in various fruits, vegetables, and nuts and it is abundant in strawberries,apple, grapes

Family:Anacardiaceae.

A flavonoid present in many fruits and vegetables, fisetin has shown promise as an epilepsy treatment agent because of its neuroprotective, anti-inflammatory, and antioxidant qualities. Its potential in experimental models of epilepsy has been examined in a number of preclinical investigations.In preclinical models of epilepsy, fisetin, a naturally occurring flavonoid present in strawberries, apples, and onions, has shown encouraging neuroprotective and anticonvulsant properties.

Neuroprotective and Anticonvulsant Properties Fisetin dramatically postponed the start of seizures and decreased their intensity in a pentylenetetrazole (PTZ)-induced kindling model in mice. Fisetin shielded neurons from apoptosis and decreased oxidative stress and neuroinflammation.[129].Modulation of Oxidative Stress and Inflammatory Pathways.The fisetin exhibits anticonvulsant effects, possibly by modulating oxidative stress and inflammation markers, which are known to play key roles in seizure pathophysiology.[130]. Oxidative Stress and Seizure Control: Fisetin pretreatment decreased lipid peroxidation and restored Na+/K+-ATPase activity in a rat model of traumatic epilepsy brought on by intracortical iron injection, suggesting protection against seizures brought on by oxidative stress.

Discussion:

A common neurological condition called epilepsy is typified by recurrent, spontaneous seizures brought on by aberrant electrical discharges in the brain. Neurotransmitter imbalances, alterations in ion channel function, genetic abnormalities, and malfunctioning brain circuitry are all part of its complicated pathogenesis. The development and spread of seizures are significantly impacted by excitatory-inhibitory imbalance, notably decreased GABA activity and increased glutamate transmission. A clinical history, neurological

examination, electroencephalogram (EEG), and neuroimaging techniques including MRI and CT scans to identify structural abnormalities in the brain are used to make the diagnosis. Treatment and management choices are influenced by the types, frequency, triggers, and underlying causes of epilepsy.

Conclusion:

With several underlying causes and clinical manifestations, epilepsy remains a complex brain disorder. Standard antiepileptic drugs can put many people into remission, but for some patients, side effects and drug resistance restrict their effectiveness. Because of their anti-inflammatory and antioxidant properties, natural compounds including Tanshinone IIA, Curcumin, Chrysin, Apigenin, Wogonin, Quercetin, and others are gaining popularity as intriguing substitutes.

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