



Biological Complexity of Epileptogenesis and the Emerging Role of Natural Molecules in Neuroprotection: A Review

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Abstract

Epilepsy, a neurologically heterogeneous disorder, affects approximately 50 million individuals globally, with a lifetime incidence of around 3 %. For example, in the United States, active epilepsy affects 1.1 % of adults. The disease has a complex biological nature, encompassing genetic factors, molecular-cellular and epigenetic mechanisms and the “triad” of oxidative stress, neuroinflammation and neuronal degeneration. Although traditional antiepileptic drugs (AEDs) provide symptomatic control, their inherent limitations, particularly in the treatment of drug-resistant epilepsy (affecting one-third of patients), as well as the lack of disease-modifying properties highlight a significant therapeutic gap. Strategies for AED use underscore the need to expand therapeutic approaches. A potential avenue in the field of pharmacological prevention today is herbal drugs, with their pleiotropic neuroprotective activity. They represent a potential area for new approaches that modulate molecular and cellular pathways. The aim of this paper was to synthesise information on this topic while discussing the potential of the phytotherapeutic approaches described to date.

Key words: Epilepsy; Epileptogenesis; Neuroprotection; Anticonvulsants; Oxidative stress; Biological products; Pharmacology.

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Introduction

Epilepsy is a complex and neurologically heterogeneous condition characterised by a persistent predisposition to spontaneous, recurrent seizures. These events arise from transient, paroxysmal disruptions in brain function caused by excessive or hypersynchronous neuronal discharges.^{1, 2} The clinical landscape is broad, varying by seizure phenotype and age of onset and reflects a wide spectrum of underlying causes, including genetic, structural, metabolic, immune and infectious factors.³

Globally, epilepsy remains a major public health challenge, affecting approximately 50 million people, with a cumulative lifetime incidence of roughly 3 %.⁴ In the United States, recent epidemiological surveys indicate that active epilepsy affects approximately 1.1 % of the adult population (about 3 million people).⁵ Despite its prevalence, diagnosis can be complicated by the limited sensitivity of standard investigations; in a proportion of patients, routine electroencephalography (EEG) and magnetic resonance imaging (MRI)

yield normal findings, which may delay therapeutic intervention.⁶

The pathophysiology of epileptogenesis is well characterised and centres on three interconnected processes: oxidative stress, neuroinflammation and progressive neuronal injury. A central node in the inflammatory arm is the high-mobility group box 1 protein (HMGB1), which, on release from stressed or dying neurons, engages Toll-like receptor 4 (TLR4) and activates downstream nuclear factor- κ B (NF- κ B) signalling, driving transcription of interleukin-1 β (IL-1 β), IL-6 and tumour necrosis factor- α (TNF- α). The cascade is accompanied by reactive astrogliosis and microglial activation and sustained cytokine exposure lowers seizure threshold and promotes the synaptic reorganisation that consolidates the epileptic network.⁷⁻⁹ In parallel, mitochondrial dysfunction and the resulting accumulation of reactive oxygen species deplete endogenous antioxidant defences, in which the nuclear factor erythroid 2-related factor 2 (Nrf2) – antioxidant response element (ARE) axis is a principal regulator.¹⁰ Because these mechanisms operate across several neurological disorders, they are not specific to epilepsy; they constitute an established biological framework against which candidate therapies can be evaluated.

Pharmacological management of epilepsy has relied on antiseizure medications (ASMs), which provide symptomatic control by modulating ion channels or neurotransmitter systems (eg voltage-gated sodium and calcium channels, gamma-aminobutyric acidergic (GABAergic) and glutamatergic signalling).¹¹ Initial treatment is typically based on monotherapy, with the choice of agent guided by seizure type, syndrome, comorbidities and tolerability. According to International League Against Epilepsy (ILAE) review, levetiracetam, zonisamide, carbamazepine and phenytoin have A level of efficacy evidence as initial monotherapy for adult focal-onset seizures, while ethosuximide and valproic acid have A level for childhood absence seizures.¹² However, a fundamental limitation of currently approved ASMs is their lack of demonstrated disease-modifying or antiepileptogenic properties; they suppress seizures without addressing the underlying progression of the disease.^{13, 14} This therapeutic gap is most evident in drug-resistant epilepsy, which affects approximately one-third of patients, with prevalence rates ranging from 13.7 % in community-based studies to 36.3 % in clinical cohorts.¹⁵

Against this background, herb-derived compounds have attracted increasing attention and the body of supporting research has expanded steadily in recent years at the intersection of pharmacognosy, neurobiology and pharmacology. Across a wide range of medicinal plants, the active constituents reported to influence seizure activity fall into a relatively small number of structural classes. Among them are flavonoids, terpenoids, isoflavones and alkaloids, many of which are already well known for their antioxidant and anti-inflammatory properties.

For example, in preclinical seizure models, the flavanone naringin (the 7-O-neohesperidoside of naringenin) has been associated with reduced activation of the HMGB1 – TLR4 pathway and lower levels of IL-1 β , IL-6 and TNF- α .¹⁶ The flavone apigenin has been linked to modulation of the phosphoinositide 3-kinase (PI3K) – protein kinase B (AKT) signalling pathway and attenuated astrocyte activation.¹⁷ Another example is kaempferol, with its regulation of AMPA-receptor – mediated calcium influx and reduced neuronal excitability.¹⁸ Related effects have been described for other classes. The isoflavone biochanin A has been reported to engage the PI3K / AKT / Nrf2 pathway and to support antioxidant enzyme activity (glutathione, superoxide dismutase and catalase), while the terpenoid amarisolide A has shown dose-dependent anticonvulsant activity attributed in part to GABAergic and serotonergic mechanisms.^{19, 20} Omega-3 long-chain fatty acids have likewise been linked to activation of the Nrf2 – antioxidant response.²¹

Taken together, these observations describe an active and rapidly developing area of investigation. The available data derive predominantly from *in vitro* and animal studies and questions of bioavailability, dosing and clinical relevance continue to be explored. It is precisely this growing convergence of pharmacological interest and emerging mechanistic data that makes a focused appraisal of plant-derived compounds in epilepsy both timely and relevant.

The aim of this research was to discuss the current biological basis of epilepsy with a focus on herb-derived drugs as a developing therapeutic direction.

Methods

A literature search was conducted across *eLibrary*, *PubMed*, *Web of Science*, *Scopus* and *Google Scholar* to identify relevant papers. The search strategy employed a combination of keywords: “epilepsy”, “epileptogenesis”, “neurodegeneration”, “neuroinflammation”, “neuroprotection”, “oxidative stress”, “antiseizure drugs” and “phyto compounds” – combined through Boolean operators within the thematic scope (Figure 1).

Retrieved records were deduplicated, after which titles and abstracts were screened and potentially relevant articles assessed in full text. The

search focused primarily on literature published between 2010 and 2026, while a limited number of earlier publications were retained where mechanistically relevant. Inclusion criteria: original research, systematic reviews and meta-analyses published in English. Exclusion criteria: non-peer-reviewed sources, conference abstracts, editorials, non-English articles and studies unrelated to the pathophysiology or pharmacological treatment of epilepsy. For each selected source, data on the relevant compounds or drug classes, experimental models, observed effects and proposed mechanisms of action were extracted.

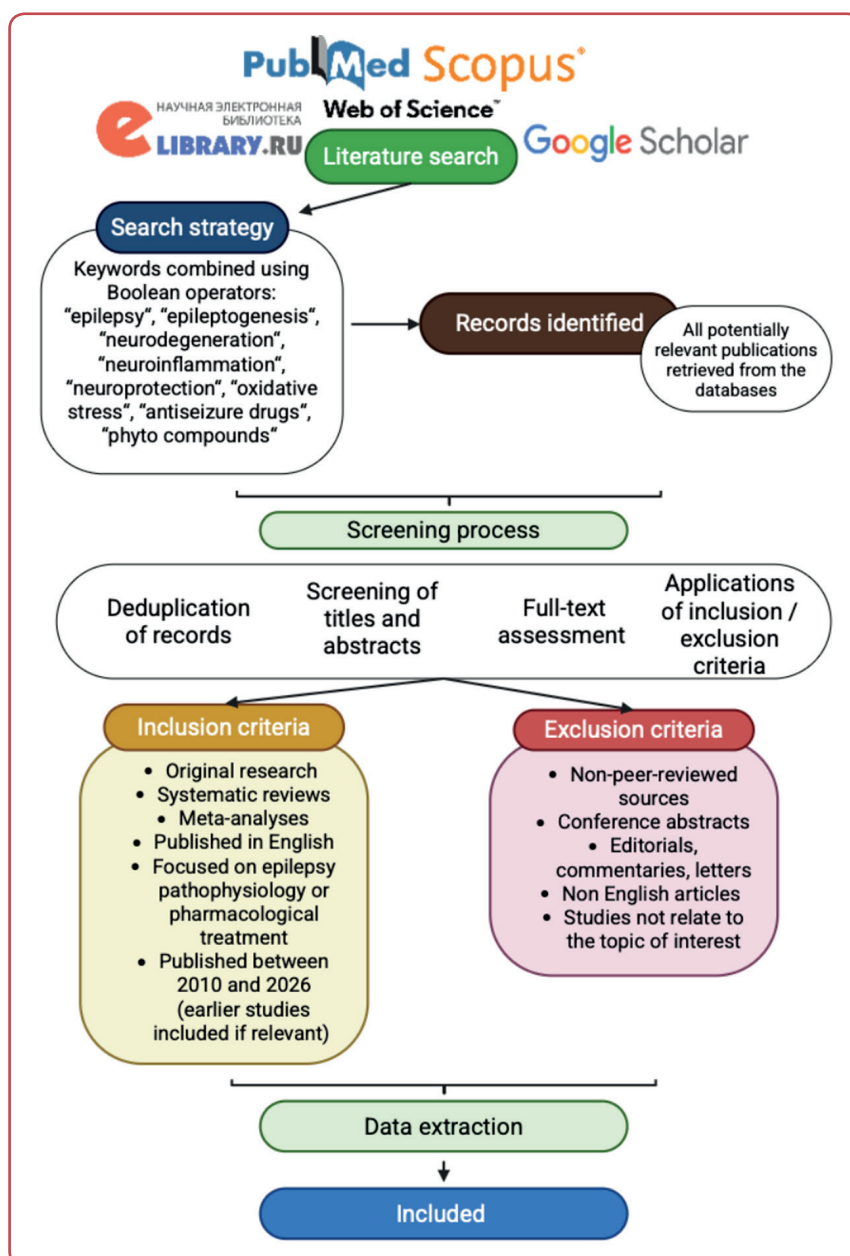


Figure 1: Overview of the literature search and selection process

The biological basis of epileptogenesis

Epileptogenesis is defined as the dynamic, progressive process by which a non-epileptic brain develops a chronic, spontaneous predisposition to generate recurrent seizures.²² This transformation involves the interplay of several factors: genetic susceptibility,^{23, 24} large-scale transcriptional remodelling,²⁵ dysregulation of intracellular signalling cascades,²⁶ persistent neuroinflammatory activation²⁷ and systemic alterations in neural network architecture.²⁸ Underlying these changes is an imbalance between excitation and inhibition (E / I), in which excessive glutamatergic signalling and weakened GABAergic restraint create a permissive environment for paroxysmal discharges.

Genetic determinants and primary channelopathies

Twin and familial studies have established that genetic factors account for up to 80 % of epilepsy cases, reflecting a high heritability.²⁹ A substantial proportion of these genetic drivers involve channelopathies: mutations in genes encoding voltage-gated or ligand-gated ion channels that alter intrinsic membrane excitability across a broad phenotypic spectrum.³⁰

For example, the *SCN1A* gene, encoding the voltage-gated sodium channel NaV1.1, represents the archetypal epilepsy-associated channelopathy. Its pathogenic variants span a clinically heterogeneous spectrum; yet converge on a shared mechanistic core in which reduced NaV1.1 function in GABAergic inhibitory interneurons disrupts cortical excitation-inhibition balance and lowers the threshold for seizure generation.^{31, 32} The degree of interneuron hypoexcitability and the extent of network disinhibition correlate with phenotypic severity: haploinsufficiency leading to near-complete loss of NaV1.1 in parvalbumin-positive fast-spiking interneurons produces the most severe seizure burden, while partial loss-of-function variants yield milder phenotypes within the same pathophysiological condition.³³ Beyond sodium channels, mutations in potassium channel genes such as *KCNQ2* and *KCNQ3*, which mediate the stabilising M-current and calcium channel genes like *CACNA1A*, underscore the diverse genetic triggers that can destabilise neuronal membrane potentials.^{34, 35}

While primary mutations provide the blueprint, epigenetic mechanisms serve as the operational “switches” (or “spotters”) that translate initial brain insults into chronic disease states. The RE-1 silencing transcription factor (REST), also known as the neuron-restrictive silencing factor (NRSF), acts as a “master regulator” in this context.³⁶ Following status epilepticus or traumatic brain injury, REST / NRSF is often upregulated, leading to the large-scale repression of genes essential for synaptic homeostasis, including those encoding HCN1 channels and GABA-A receptor subunits.^{37, 38} This epigenetic remodelling is further modulated by DNA methylation and microRNA-mediated silencing, which together orchestrate the progressive shift toward a pro-epileptic transcriptome.³⁹

Biological consequences of seizures and molecular foundations for phytotherapy

Chronic seizure activity acts on the brain not merely through acute neuronal injury but through the sustained dysregulation of conserved signalling networks. Central among these is the mechanistic target of rapamycin complex 1 (mTORC1, Figure 2).⁴⁰

mTORC1 hyperactivation is not confined to monogenic syndromes like tuberous sclerosis complex (TSC); somatic mutations in the upstream activators AKT3, MTOR, PIK3CA and RHEB, as well as germline variants in the GATOR1 complex subunits DEPDC5, NPRL2 and NPRL3, collectively define a broader class of “mTORopathies” (focal cortical dysplasias and related malformations of cortical development that account for a substantial proportion of pharmacoresistant focal epilepsies).^{41, 42} In recent work by Proietti Onori M, et al (2021), mTOR-dependent seizures were shown to arise primarily through enhanced axonal connectivity and downstream hyperexcitability of distally connected neurons, rather than through local malformation alone.⁴³

A further dimension of complexity emerges from the relationship between mTOR, Wnt signalling and metabolic reprogramming. Early in the post-insult epileptogenic period, coordinated activation of Wnt-driven aerobic glycolysis, precedes mTOR activation and appears to lie upstream of it; blocking this glycolytic programme with 2-deoxyglucose reduces mTOR activation and attenuates seizure development.⁴⁴ The downstream consequences of mTOR hyperactivation are inti-

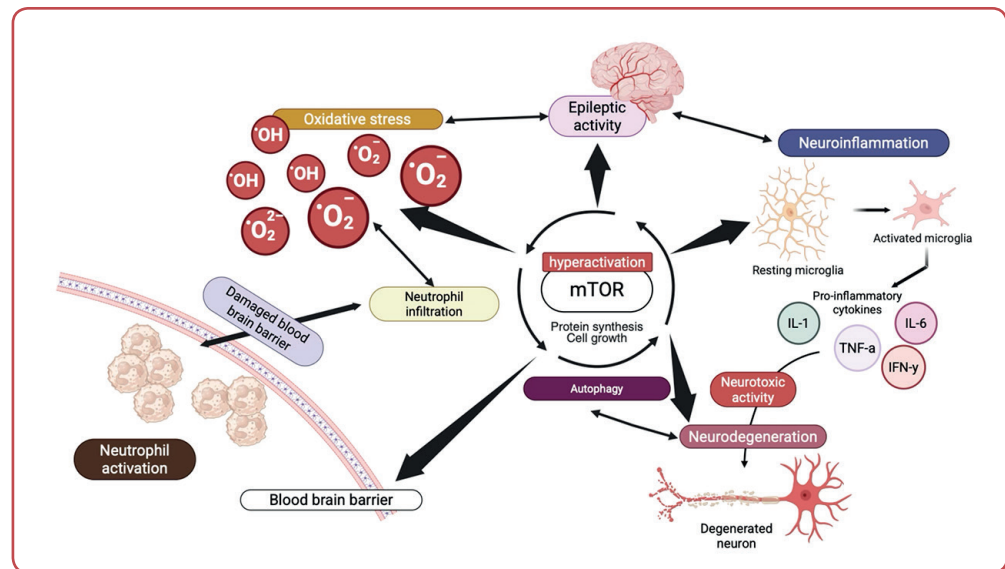


Figure 2: Central role of mechanistic target of rapamycin (mTOR) hyperactivation in the pathophysiological “triad” of epilepsy

Aberrant hyperactivation of the mammalian target of rapamycin (mTOR), a key regulator of protein synthesis, cell growth and autophagy, establishes a self-reinforcing network linking epileptic activity, neuroinflammation and neurodegeneration. Upstream, mTOR hyperactivation drives excessive reactive oxygen species (ROS) generation: superoxide ($\text{O}_2^{\cdot-}$) and hydroxyl radicals ($\text{OH}^{\cdot}$), creating an oxidative environment that compromises blood-brain barrier integrity and facilitates peripheral neutrophil infiltration into the central nervous system. In parallel, mTOR-driven signalling promotes the transition of resting microglia to an activated phenotype, sustaining the release of pro-inflammatory cytokines (eg IL-1, TNF- α , IL-6 and IFN- γ), that amplify excitotoxic injury and impair autophagic clearance of damaged cellular components. Disrupted autophagy, itself a downstream consequence of mTOR dysregulation, further accelerates neurotoxic activity and progressive neuronal loss.

mately connected to three overlapping forms of regulated neuronal death: apoptosis, necroptosis and ferroptosis, whose relative contributions to the epileptic brain and whose boundaries as distinct biological processes, remain subjects of active investigation.

Apoptosis via caspase-3 activation represents a pathway of excitotoxic neuronal loss, but growing evidence indicates that iron-dependent lipid peroxidation, the defining feature of ferroptosis, operates in parallel and may in certain contexts predominate. In kainic-acid models of temporal lobe epilepsy, hippocampal ferroptosis is measurable through markers of lipid peroxidation and mitochondrial structural collapse and its inhibition through the Nrf2 / GPX4 signalling axis reduces neuronal loss and cognitive impairment.⁴⁵ Critically, the Keap1 / Nrf2 / GPX4 axis represents a point of convergence between ferroptosis and oxidative stress more broadly. For example, Nrf2 activation suppresses both lipid peroxidation-driven ferroptosis and reactive oxygen species (ROS)-mediated apoptosis simultaneously, suggesting that these pathways share executioner machinery rather than operating as fully independent processes.⁴⁶

Necroptosis, mediated by the RIPK1 / RIPK3 / MLKL cascade, adds a further layer of complexity. The concurrence of ferroptosis and neuroinflammation in the epileptic hippocampus appears to be maintained through shared regulatory nodes including SIRT1, Nrf2, NF- κ B and COX-2, with activated microglia and astrocytes both responding to and amplifying ferroptotic signals through inflammatory lipid mediators.⁴⁷

The transition from a self-limiting seizure to self-sustaining status epilepticus represents a distinct and therapeutically critical phase. Within minutes of seizure onset, a coordinated and bidirectional receptor trafficking event reshapes synaptic composition: γ 2-subunit-containing GABA-A receptors are internalised through clathrin-dependent endocytosis, reducing synaptic inhibitory efficacy. The NR2B-containing NMDA receptors and calcium-permeable GluA2-lacking AMPA receptors simultaneously traffic to the synaptic membrane, amplifying excitatory drive.⁴⁸

Similarly, the modulation of brain-derived neurotrophic factor (BDNF) and its receptor TrkB is essential for regulating synaptic plasticity and

preventing the aberrant network reorganisation, as mossy fibre sprouting, that sustains chronic epilepsy.⁴⁹ Furthermore, emerging research on the gut-brain axis suggests that modulating the microbiome through dietary interventions or specific phytochemicals could offer novel avenues for epilepsy management, influencing neuroinflammation and neurotransmitter balance.^{50, 51}

Structural and functional brain alterations associated with epilepsy

Epilepsy is characterised by a constellation of structural and functional alterations within the brain. The changes collectively contribute to the establishment and perpetuation of the epileptic state.⁵² One of the most recognised macroscopic structural alterations in epilepsy is hippocampal sclerosis (HS), particularly prevalent in mesial temporal lobe epilepsy (MTLE). HS is characterised by significant neuronal loss, predominantly in the CA1 and CA3 subfields of the hippocampus, accompanied by reactive astrogliosis and microglial activation.⁵³ It is important to note that the neuronal degeneration is not uniform; rather, it exhibits a selective vulnerability, leading to profound reorganisation of hippocampal circuitry (Figure 3). Neuroimaging studies, particularly

high-resolution MRI, consistently reveal hippocampal atrophy and altered signal intensity in patients with MTLE and HS.⁵⁴⁻⁵⁶ Beyond the hippocampus, epilepsy can induce more widespread cortical changes (eg cortical thinning and altered cortical folding patterns), which are indicative of underlying neuronal loss or aberrant development. These cortical alterations often correlate with seizure frequency, cognitive deficits and disease duration, suggesting their active role in disease progression.^{57, 58}

Furthermore, white matter tract disruptions are increasingly recognised as critical structural substrates. For example, diffusion tensor imaging (DTI) studies frequently demonstrate reduced fractional anisotropy and increased mean diffusivity in various white matter tracts, reflecting demyelination, axonal damage and altered connectivity.⁵⁹ The white matter abnormalities are often observed in regions functionally connected to the primary seizure focus, highlighting the widespread impact of epilepsy on brain structural integrity.⁶⁰

At the microscopic level, epileptogenesis involves intricate cellular and synaptic reorganisation. Dendritic spine loss and alterations in spine morphology are prominent features, particularly in hippocampal and cortical neurons.^{61, 62} These changes directly impact synaptic plasticity and excitatory neurotransmission (that links to the

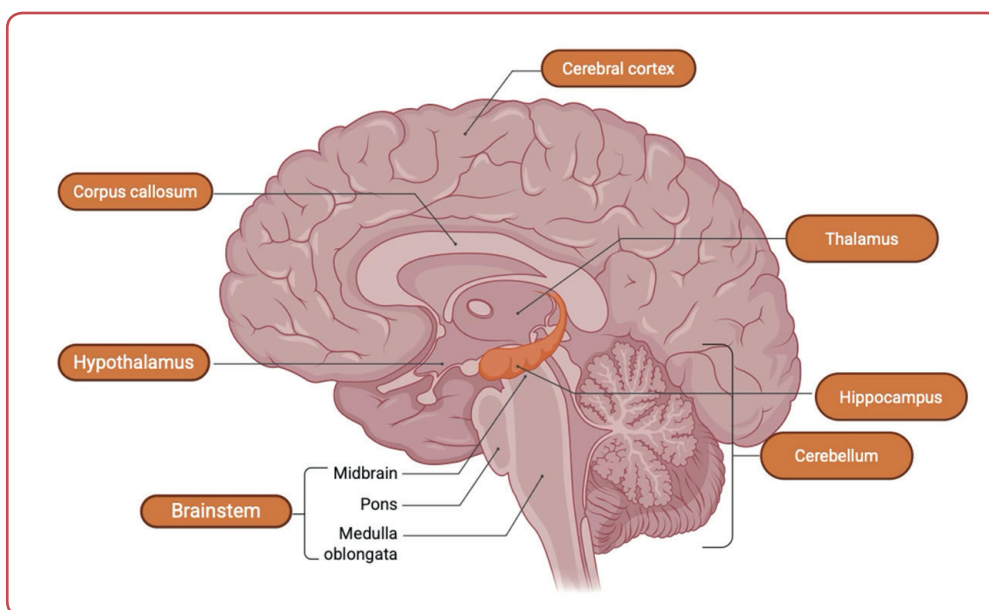


Figure 3: Midsagittal anatomy of the human brain indicating structures implicated in epilepsy-associated structural and functional pathology. Anatomical illustration adapted for educational orientation; hippocampal subfield detail not shown at this scale

hyperexcitable state).⁶³ Conversely, mossy fibre sprouting, an aberrant growth of dentate granule cell axons into the inner molecular layer of the dentate gyrus, is a hallmark of MTLE.⁶⁴ While its precise role in epileptogenesis remains debated, it is hypothesised to form recurrent excitatory circuits, thereby promoting seizure generation. On the other hand, astrogliosis, characterised by the hypertrophy and proliferation of astrocytes, is another ubiquitous pathological feature. Activated astrocytes undergo significant morphological and functional changes: altered glutamate uptake, impaired potassium buffering, increased release of pro-inflammatory mediators and others – all of which contribute to neuronal hyperexcitability and neuroinflammation. Microglial activation also plays a crucial role, contributing to both neuroinflammation and synaptic pruning, further reshaping neural circuits.^{65–67}

A critical functional alteration is the breakdown of the blood-brain barrier (BBB). Chronic seizure activity and associated neuroinflammation can compromise BBB integrity and lead to extravasation of albumin and other serum proteins into the brain parenchyma.^{68, 69} The BBB dysfunction can directly contribute to neuronal hyperexcitability by altering the extracellular ionic environment, activating astrocytes and promoting neuroinflammation, thereby creating a vicious cycle that perpetuates epileptogenesis.⁷⁰ The regional vulnerability of structures like the hippocampus and temporal lobe to epileptic insults is partly explained by their unique physiological properties, including high synaptic plasticity and susceptibility to excitotoxic damage, making them prime candidates for the initiation and propagation of seizures.⁷¹

In summary, the structural and functional brain alterations in epilepsy are multifaceted and interconnected, ranging from gross anatomical changes like hippocampal sclerosis to subtle molecular and cellular dysregulations.

Current and emerging therapeutic strategies for epilepsy

For most of its regulatory history, the clinical evaluation of drugs for epilepsy was defined by a reduction in seizure frequency. The adoption in

September 2025 of a revised European Medicines Agency guideline on the clinical investigation of medicinal products in epileptic disorders marks a substantive departure from that reductive standard.³ The revision integrates the 2017 ILAE seizure classification in full, replacing the term “antiepileptic drug” with “antiseizure medication” (ASM) throughout.⁷²

The scope of the guideline has been correspondingly broadened: where the 2010 version devoted fewer than three lines to status epilepticus and provided no specific guidance on neonatal seizures, the 2025 revision introduces dedicated sections on both, together with expanded provisions for developmental and epileptic encephalopathies. Of equal translational significance is the redefinition of efficacy itself: cognitive, neuromotor, behavioural and patient-reported outcomes are now formally incorporated as co-primary and secondary endpoints.⁷³ Approved ASMs achieve sustained seizure freedom in approximately two-thirds of patients; for the remaining third, drug resistance persists despite sequential trials of multiple agents and no licensed compound has yet demonstrated unambiguous antiepileptogenic activity, the capacity to prevent or modify the underlying disease process in controlled human trials.^{74, 75}

Approved ASMs are pharmacologically diverse.⁷⁶ Carbamazepine and phenytoin stabilise membrane excitability through use-dependent blockade of voltage-gated sodium channels. Lacosamide selectively enhances their slow inactivation state – a kinetically distinct gating mode preferentially engaged during sustained ictal depolarisations.⁷⁷ GABAergic agents act through separable routes: benzodiazepines potentiate GABA-A receptor chloride conductance; phenobarbital prolongs channel open time and valproate elevates synaptic GABA availability through inhibition of its principal catabolic enzymes.⁷⁸

Among more recently approved compounds, perampanel selectively antagonises AMPA-type ionotropic glutamate receptors, attenuating excitatory drive, while levetiracetam and brivaracetam exert their effects through high-affinity binding to the synaptic vesicle glycoprotein SV2A – it is a presynaptic target mechanistically unrelated to any ion channel or classical receptor system.^{79, 80} Despite this mechanistic breadth, a prospective cohort study by Kwan and Brodie established that approximately one-third of patients do not achieve sustained seizure freedom regardless of

the number or sequence of agents employed (a proportion that has not changed substantially with subsequent drug generations).⁸¹

Preliminarily, the basis of this pharmacoresistance encompasses overexpression of efflux transporters at the blood-brain barrier, adaptive modification of ASM binding targets and progressive network reorganisation.

Natural bioactive molecules in neuroprotective strategies for epilepsy

The challenge of drug-resistant epilepsy has catalysed extensive research into natural bioactive molecules. These compounds, often sourced from plants and fungi, represent a rich pharmacopeia of diverse chemical structures possessing pleiotropic pharmacological activities. The “phytodrugs” have antioxidant, anti-inflammatory, anti-excitotoxic and other pharmacological properties that align with the molecular and cellular points of neuronal degeneration previously established and offer a prospective avenue to modulate epileptogenesis and mitigate neuronal damage.

A systematic review by Sharifi-Rad et al examined the antiepileptic properties of plant-derived bioactive molecules across flavonoids, alkaloids and terpenoids. Authors demonstrated that each class engages molecular targets overlapping with those of approved ASMs. Among flavonoids, quercetin (2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy-4H-chromen-4-one) emerged as a compound of particular interest: the catechol moiety of its B-ring confers iron-chelating and radical-scavenging capacity, while the planar chromone scaffold facilitates allosteric interaction with GABA-A receptor benzodiazepine-binding sites, collectively attenuating both oxidative neuronal injury and GABAergic transmission deficits relevant to epileptogenesis. In addition, alkaloids, whose nitrogen-containing heterocyclic structures confer pronounced affinity for ionotropic receptors, were shown to modulate NMDA receptor-mediated excitation and to inhibit voltage-gated sodium channels through binding modes mechanistically distinct from those of phenytoin or carbamazepine. Terpenoids, as lipophilic isoprenoid-derived scaffolds, demonstrated capacity to influence membrane fluidity and ion channel gating in a concentration-dependent manner.⁸²

He et al conducted a focused review of medicinal plant constituents evaluated in preclinical seizure models between 2018 and 2023. Re-

searchers found sixty natural products with anticonvulsant activity from eighty plant species used in traditional practice across African and Asian regions. The pharmacological effects of the compounds were attributable to four primary mechanisms: modulation of GABAergic and glutamatergic transmission, antioxidant activity, anti-neuroinflammatory effects and direct neuroprotection, with several constituents demonstrating activity across more than one pathway simultaneously. Flavonoids (eg baicalin, apigenin and luteolin) were among the most consistently represented, alongside alkaloids as berberine and terpenoid-derived compounds. It underscores the chemical diversity of the preclinical evidence base.⁸³ However, it is important to note that, while the vast majority of the identified compounds are promising, there is currently a lack of research confirming their metabolic stability, toxicological profile and clinical application. In another work by Pradhan et al, authors catalogued the broad panel of flavonoids (eg quercetin, rutin, apigenin, luteolin, morin, fisetin, kaempferol, wogonin) across experimental epilepsy models, demonstrating modulation of NMDA and AMPA receptor-mediated excitatory drive, restoration of GABA-mediated inhibitory tone, inhibition of NF- κ B pathway neuroinflammatory signalling and suppression of seizure-associated oxidative damage.⁸⁴ Alhamhoom et al explored nanoformulation as a strategy to address the pharmacokinetic limitations of this compound class. Authors demonstrated, in a pentylenetetrazole (PTZ) induced rat model, that apigenin- and quercetin-rich silver nanoparticles synthesised from *Matricaria chamomilla* extract outperformed the parent crude extract across multiple seizure endpoints (seizure latency, frequency and duration), restored hippocampal GABA concentrations and reduced oxidative stress markers.⁸⁵ This effect was attributed to the enhanced bioavailability and prolonged brain residence afforded by nano-encapsulation.

The other findings in literature indicate that natural compounds, for example resveratrol, a polyphenol abundant in grapes, exhibit antidepressant effects and contributes to neuronal resilience, a factor highly relevant to epilepsy-associated comorbidities.⁸⁶ This observation aligns with research by Waris et al, who further explored the neuroprotective efficacy of compounds like spicatoside and resveratrol, among other plant extracts. Their studies suggest these natural agents attenuate neurological damage and confer protective benefits against diverse neurological

insults pertinent to epileptogenesis.⁸⁷ The consistent demonstration of resveratrol's neuroprotective properties across independent investigations, despite variations in experimental models or endpoints, supports its therapeutic potential.

Fungal derivatives also present a compelling area of investigation. Kou et al successfully isolated and characterised novel triterpenoids from *Inonotus obliquus*, a medicinal mushroom. This study advances understanding of the chemical diversity within this fungus, renowned for its medicinal properties.⁸⁸ Expanding on this, Wang et al specifically investigated 2 α -hydroxy-3 β -acetoxy-lanosta-8,24-dien-21-oic acid (2 α -HI), a compound derived from *Inonotus obliquus*. The *in vitro* research demonstrated that 2 α -HI protects against H₂O₂-induced oxidative stress and apoptosis; it provides mechanistic insights into its potential to mitigate neuronal damage in conditions like epilepsy, but further *in vivo* validation remains essential to bridge the gap to clinical applicability.⁸⁹ Concurrently, Bonetto et al reviewed fungal bioactive compounds as therapeutic options for age-related neurodegenerative disorders. The authors cited *Inonotus obliquus* extracts for their neuroprotective potential and highlighted the escalating interest in fungal metabolites for promoting brain health and combating neurodegeneration.⁹⁰

Taken together, this review reflects a mature understanding of epilepsy as a multidimensional neurological disorder. Nevertheless, further research is needed in the field of pharmacological prevention. To date, the growing body of preclinical data on natural bioactive compounds, particularly polyphenolic and alkaloid molecules, suggests that these agents may be positioned not as replacements for approved antiepileptic drugs, but as additional candidates capable of addressing neuroprotective and antiepileptic targets that are currently insufficiently addressed by pharmacotherapy. However, realising this potential will require a targeted expansion of research: validation of experimental models, establishment of the pharmacokinetic parameters necessary for a meaningful effect on the brain and integration of the perspectives of molecular pharmacologists, clinical neurologists and regulatory experts through collaborative projects capable of ensuring a complete translational continuum from preclinical proof of concept to controlled clinical evaluation.

Conclusion

In this review, the key aspects of epilepsy, a neurological disorder that is complex in terms of therapeutic approaches were highlighted. The aetiological landscape was explored, as were the pathophysiological profile of epilepsy and the pharmacological approaches to its treatment, including recent developments in herbal medicines.

Continuous advancements in understanding epileptogenesis reveal an expanding repertoire of molecular targets and therapeutic pathways. The burgeoning field of natural bioactive molecules, with their neuroprotective properties, offers a potential frontier for additional interventions. Flavonoids, alkaloids, terpenoids, polyphenols and fungal triterpenoids converge on the molecular nodes that underlie epileptogenesis and their pharmacological, multi-target action sets them apart from conventional antiseizure medications, which control symptoms without altering disease progression. On current evidence, these compounds are best regarded as neuroprotective, potentially disease-modifying drugs. Ultimately, effective epilepsy management demands an integrated, forward-thinking approach.

Researchers must continue to embrace a broad perspective in neurotherapy, recognising the disease's intricate and multi-layered impact on all levels of biological organisation. Sustained investigation into both established and emerging therapeutic modalities, particularly those offering disease modification and neuroprotection, will pave the way for more comprehensive and personalised interventions, fundamentally transforming the lives of people affected by the disease.

Ethics

This study was a secondary analysis based on the currently existing data and did not directly involve human participants or experimental animals. Therefore, the ethics approval was not required in this paper.

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Conflicts of interest

The authors declare that there is no conflict of interest.

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Data access

The data that support the findings of this study are available from the corresponding author upon reasonable individual request.

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References

1. Avanzini G, Franceschetti S. Cellular biology of epileptogenesis. *Lancet Neurol*. 2003 Jan;2(1):33-42. doi: 10.1016/s1474-4422(03)00265-5.
2. Stafstrom CE, Carmant L. Seizures and epilepsy: an overview for neuroscientists. *Cold Spring Harb Perspect Med*. 2015 Jun 1;5(6):a022426. doi: 10.1101/cshperspect.a022426.
3. European Medicines Agency [Internet]. Guideline on clinical investigation of medicinal products in the treatment of epileptic disorders. Committee for Medicinal Products for Human Use (CHMP); 2025. [Cited: 13 February 2026]. Available at: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-investigation-medicinal-products-treatment-epileptic-disorders-revision-3_en.pdf.
4. Shan T, Zhu Y, Fan H, Liu Z, Xie J, Li M, et al. Global, regional, and national time trends in the burden of epilepsy, 1990-2019: an age-period-cohort analysis for the global burden of disease 2019 study. *Front Neurol*. 2024 Aug 15;15:1418926. doi: 10.3389/fneur.2024.1418926.
5. Kobau R, Luncheon C, Greenlund K. Active epilepsy prevalence among U.S. adults is 1.1% and differs by educational level-National Health Interview Survey, United States, 2021. *Epilepsy Behav*. 2023 May;142:109180. doi: 10.1016/j.yebeh.2023.109180.
6. Khan MT, Muhammad N, Khan MR, Bai M, Rai P. Overcoming diagnostic uncertainty: a case of temporal lobe epilepsy with normal MRI and EEG. *Cureus*. 2024 Oct 9;16(10):e71125. doi: 10.7759/cureus.71125.
7. Yang H, Wang H, Andersson U. Targeting inflammation driven by HMGB1. *Front Immunol*. 2020 Mar 20;11:484. doi: 10.3389/fimmu.2020.00484.
8. Xiao L, Yan J, Feng D, Ye S, Yang T, Wei H, et al. Critical role of TLR4 on the microglia activation induced by maternal LPS exposure leading to ASD-like behavior of offspring. *Front Cell Dev Biol*. 2021 Mar 4;9:634837. doi: 10.3389/fcell.2021.634837.
9. Sanz P, Garcia-Gimeno MA. Reactive glia inflammatory signaling pathways and epilepsy. *Int J Mol Sci*. 2020 Jun 8;21(11):4096. doi: 10.3390/ijms21114096.
10. Brandes MS, Gray NE. NRF2 as a therapeutic target in neurodegenerative diseases. *ASN Neuro*. 2020 Jan-Dec;12:1759091419899782. doi: 10.1177/1759091419899782.
11. Sills GJ, Rogawski MA. Mechanisms of action of currently used antiseizure drugs. *Neuropharmacology*. 2020 May 15;168:107966. doi: 10.1016/j.neuropharm.2020.107966.

12. Glauser T, Ben-Menachem E, Bourgeois B, Cnaan A, Guerreiro C, Kälviäinen R, et al; ILAE Subcommission on AED Guidelines. Updated ILAE evidence review of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes. *Epilepsia*. 2013 Mar;54(3):551-63. doi: 10.1111/epi.12074.
13. Löscher W, Klein P. The Pharmacology and clinical efficacy of antiseizure medications: from bromide salts to cenobamate and beyond. *CNS Drugs*. 2021 Sep;35(9):935-63. doi: 10.1007/s40263-021-00827-8.
14. Galanopoulou AS, Löscher W, Lubbers L, O'Brien TJ, Staley K, et al. Antiepileptogenesis and disease modification: Progress, challenges, and the path forward-Report of the Preclinical Working Group of the 2018 NINDS-sponsored antiepileptogenesis and disease modification workshop. *Epilepsia Open*. 2021 Jun;6(2):276-96. doi: 10.1002/epi4.12490.
15. Sultana B, Panzini MA, Veilleux Carpentier A, Comtois J, Rioux B, et al. Incidence and prevalence of drug-resistant epilepsy: a systematic review and meta-analysis. *Neurology*. 2021 Apr 27;96(17):805-17. doi: 10.1212/WNL.00000000000011839.
16. Khan P, Saha N, Nidhi. Neuroprotective effect of naringin by modulation of klotho and HMGB1- TLR4 axis in PTZ-induced kindling in mice. *Biochem Biophys Res Commun*. 2025 Jan;742:151080. doi: 10.1016/j.bbrc.2024.151080.
17. Xie Z, Zhao Y, Wang Y, Song W, Li G. Apigenin regulating PI3K/AKT pathway to improve depressive behavior in epileptic rats. *Comb Chem High Throughput Screen*. 2025 Jun 23. doi: 10.2174/0113862073385668250601082232.
18. Zhao J, Qin X, Yang L, Guo H, Chen S, Tian K, et al. Application of TCM network pharmacology and experimental verification to explore the mechanism of kaempferol against epilepsy. *Brain Res Bull*. 2025 Jan;220:111150. doi: 10.1016/j.brainresbull.2024.111150.
19. Kongsui R, Promsrisuk T, Chanmanee T, Klimaschewski L, Jamsuwan S, Sriraksa N, et al. Biochanin A prevents neurodegeneration and oxidative stress in a kainic acid model of epilepsy by activating the PI3K/Akt/Nrf2 signaling pathway. *Sci Rep*. 2025 Nov 13;15(1):39842. doi: 10.1038/s41598-025-23414-z.
20. Mendoza-Madrigal R, González-Trujano ME, Onofre-Campos D, Moreno-Pérez GF, Castellanos-Mijangos JG, Martínez-Vargas D. Electroencephalographic profile of *Salvia amarissima* Ortega and *amarisolide A* in the absence and presence of PTZ-induced seizures in mice. *Biomed Pharmacother*. 2024 Apr;173:116352. doi: 10.1016/j.biopha.2024.116352.
21. Li M, Li Z, Fan Y. Omega-3 fatty acids: multi-target mechanisms and therapeutic applications in neurodevelopmental disorders and epilepsy. *Front Nutr*. 2025 May 30;12:1598588. doi: 10.3389/fnut.2025.1598588.
22. Rakhade SN, Jensen FE. Epileptogenesis in the immature brain: emerging mechanisms. *Nat Rev Neurol*. 2009 Jul;5(7):380-91. doi: 10.1038/nrneurol.2009.80.
23. Ottman R, Lee JH, Risch N, Hauser WA, Susser M. Clinical indicators of genetic susceptibility to epilepsy. *Epilepsia*. 1996 Apr;37(4):353-61. doi: 10.1111/j.1528-1157.1996.tb00571.x.
24. Dwivedi R, Kaushik M, Tripathi M, Dada R, Tiwari P. Unraveling the genetic basis of epilepsy: Recent advances and implications for diagnosis and treatment. *Brain Res*. 2024 Nov 15;1843:149120. doi: 10.1016/j.brainres.2024.149120.
25. Zaruha AG, Codreanu P, Coman MC, Novac Ii MA, Duțălon SG, Jugănaru IR, et al. Genetic-epigenetic interplay in epilepsy: pathways, biomarkers, and epigenome-targeted therapies. *Epigenomes*. 2026 Feb 10;10(1):10. doi: 10.3390/epigenomes10010010.
26. Stöber TM, Batulin D, Triesch J, Narayanan R, Jedlicka P. Degeneracy in epilepsy: multiple routes to hyperexcitable brain circuits and their repair. *Commun Biol*. 2023 May 3;6(1):479. doi: 10.1038/s42003-023-04823-0.
27. Solanki P, Jha S. Innate immune activation and neuroinflammatory pathways in Epilepsy. *Cytokine Growth Factor Rev*. 2025 Aug;84:35-46. doi: 10.1016/j.cytogfr.2025.06.009.
28. Larivière S, Royer J, Rodríguez-Cruces R, Paquola C, Caligiuri ME, et al. Structural network alterations in focal and generalised epilepsy assessed in a world-wide ENIGMA study follow axes of epilepsy risk gene expression. *Nat Commun*. 2022 Jul 27;13(1):4320. doi: 10.1038/s41467-022-31730-5.
29. Johnson MR, Milne RL, Torn-Broers Y, Hopper JL, Scheffer IE, Berkovic SF. A twin study of genetic influences on epilepsy outcome. *Twin Res*. 2003 Apr;6(2):140-6. doi: 10.1375/136905203321536263.
30. Bartolini E, Campostrini R, Kiferle L, Pradella S, Rosati E, Chinthapalli K, et al. Epilepsy and brain channelopathies from infancy to adulthood. *Neurol Sci*. 2020 Apr;41(4):749-61. doi: 10.1007/s10072-019-04190-x.
31. Scheffer IE, Nabbout R. SCN1A-related phenotypes: Epilepsy and beyond. *Epilepsia*. 2019 Dec;60 Suppl 3:S17-S24. doi: 10.1111/epi.16386.
32. Brunklaus A, Brünger T, Feng T, Fons C, Lehtikainen A, et al. The gain of function SCN1A disorder spectrum: novel epilepsy phenotypes and therapeutic implications. *Brain*. 2022 Nov 21;145(11):3816-31. doi: 10.1093/brain/awac210.
33. van Hughte EJH, Lewerissa EI, Wu KM, Scheefhals N, Parodi G, van Voorst TW, et al. SCN1A-deficient excitatory neuronal networks display mutation-specific phenotypes. *Brain*. 2023 Dec 1;146(12):5153-67. doi: 10.1093/brain/awad245.
34. Mucha M, Ooi L, Linley JE, Mordaka P, Dalle C, et al. Transcriptional control of KCNQ channel genes and the regulation of neuronal excitability. *J Neurosci*. 2010 Oct 6;30(40):13235-45. doi: 10.1523/JNEUROSCI.1981-10.2010.
35. Szymanowicz O, Drużdż A, Słowikowski B, Pawlak S, Potocka E, et al. A Review of the CACNA Gene Family: Its Role in Neurological Disorders. *Diseases*. 2024 May 5;12(5):90. doi: 10.3390/diseases12050090.
36. Mozzi A, Guerini FR, Forni D, Costa AS, Nemni R, Baglio F, et al. REST, a master regulator of neurogenesis, evolved under strong positive selection in humans and in non human primates. *Sci Rep*. 2017 Aug 25;7(1):9530. doi: 10.1038/s41598-017-10245-w.
37. Hall AM, Kamei N, Shao M, Mun HS, Chen K, Chen Y, et al. Inhibition of neuron-restrictive silencing factor (REST/NRSF) chromatin binding attenuates Epileptogenesis. *eNeuro*. 2024 May 17;11(5):ENEURO.0006-24.2024. doi: 10.1523/ENEURO.0006-24.2024.
38. Chmielewska N, Wawer A, Maciejak P, Turzyńska D, Sobolewska A, et al. The role of REST/NRSF, TrkB and

- BDNF in neurobiological mechanisms of different susceptibility to seizure in a PTZ model of epilepsy. *Brain Res Bull.* 2020 May;158:108-115. doi: 10.1016/j.brainresbull.2020.03.007.
39. Brennan GP, Henshall DC. MicroRNAs as regulators of brain function and targets for treatment of epilepsy. *Nat Rev Neurol.* 2020 Sep;16(9):506-19. doi: 10.1038/s41582-020-0369-8.
 40. Gerasimenko A, Baldassari S, Baulac S. mTOR pathway: Insights into an established pathway for brain mosaicism in epilepsy. *Neurobiol Dis.* 2023 Jun 15;182:106144. doi: 10.1016/j.nbd.2023.106144.
 41. Moloney PB, Cavalleri GL, Delanty N. Epilepsy in the mTORopathies: opportunities for precision medicine. *Brain Commun.* 2021 Sep 25;3(4):fcab222. doi: 10.1093/braincomms/fcab222.
 42. Dawson RE, Nieto Guil AF, Robertson LJ, Piltz SG, Hughes JN, Thomas PQ. Functional screening of GATOR1 complex variants reveals a role for mTORC1 deregulation in FCD and focal epilepsy. *Neurobiol Dis.* 2020 Feb;134:104640. doi: 10.1016/j.nbd.2019.104640.
 43. Proietti Onori M, Koene LMC, Schäfer CB, Nellist M, de Brito van Velze M, Gao Z, et al. RHEB/mTOR hyperactivity causes cortical malformations and epileptic seizures through increased axonal connectivity. *PLoS Biol.* 2021 May 26;19(5):e3001279. doi: 10.1371/journal.pbio.3001279.
 44. Alqurashi RS, Yee AS, Malone T, Alrubiaan S, Tam MW, Wang K, et al. A Warburg-like metabolic program coordinates Wnt, AMPK, and mTOR signaling pathways in epileptogenesis. *PLoS One.* 2021 Aug 6;16(8):e0252282. doi: 10.1371/journal.pone.0252282.
 45. Chen S, Zhao L, Jin X, Liu Q, Xiao Y, Xu H. Astaxanthin inhibits ferroptosis of hippocampal neurons in kainic acid-induced epileptic mice by activating the Nrf2/GPX4 signaling pathway. *CNS Neurosci Ther.* 2025 Feb;31(2):e70238. doi: 10.1111/cns.70238.
 46. Wang D, Cui Y, Gao F, Zheng W, Li J, Xian Z. Keap1/Nrf2 signaling pathway participating in the progression of epilepsy via regulation of oxidative stress and ferroptosis in neurons. *Clinics (Sao Paulo).* 2024 May 10;79:100372. doi: 10.1016/j.clinsp.2024.100372.
 47. Xu Y, Jia B, Li J, Li Q, Luo C. The interplay between ferroptosis and neuroinflammation in central neurological disorders. *Antioxidants (Basel).* 2024 Mar 26;13(4):395. doi: 10.3390/antiox13040395.
 48. Wasterlain C. Fifty years of research on status epilepticus: Seizures use hippocampal memory circuits to generate status epilepticus and disrupt brain development. *Epilepsy Behav.* 2023 Apr;141:109142. doi: 10.1016/j.yebeh.2023.109142.
 49. Ben-Ari Y. Cell death and synaptic reorganizations produced by seizures. *Epilepsia.* 2001;42 Suppl 3:5-7. doi: 10.1046/j.1528-1157.2001.042suppl.3005.x.
 50. Nakhal MM, Yassin LK, Alyaqoubi R, Saeed S, Alderei A, et al. The microbiota-gut-brain axis and neurological disorders: a comprehensive review. *Life (Basel).* 2024 Sep 26;14(10):1234. doi: 10.3390/life14101234.
 51. Villavicencio-Tejo F, Olesen MA, Navarro L, Calisto N, Iribarren C, García K, et al. Gut-Brain Axis Deregulation and Its Possible Contribution to Neurodegenerative Disorders. *Neurotox Res.* 2023 Dec 16;42(1):4. doi: 10.1007/s12640-023-00681-0.
 52. Turker S, Severcan M, Ilbay G, Severcan F. Epileptic seizures induce structural and functional alterations on brain tissue membranes. *Biochim Biophys Acta.* 2014 Dec;1838(12):3088-96. doi: 10.1016/j.bbame.2014.08.025.
 53. Thom M. Review: Hippocampal sclerosis in epilepsy: a neuropathology review. *Neuropathol Appl Neurobiol.* 2014 Aug;40(5):520-43. doi: 10.1111/nan.12150.
 54. Memarian N, Thompson PM, Engel J Jr, Staba RJ. Quantitative analysis of structural neuroimaging of mesial temporal lobe epilepsy. *Imaging Med.* 2013 Jun 1;5(3):10.2217/iim.13.28. doi: 10.2217/iim.13.28.
 55. Shih YC, Tseng CE, Lin FH, Liou HH, Tseng WY. Hippocampal atrophy is associated with altered hippocampus-posterior cingulate cortex connectivity in mesial temporal lobe epilepsy with hippocampal sclerosis. *AJNR Am J Neuroradiol.* 2017 Mar;38(3):626-32. doi: 10.3174/ajnr.A5039.
 56. Duan Y, Lin Y, Rosen D, Du J, He L, Wang Y. Identifying morphological patterns of hippocampal atrophy in patients with mesial temporal lobe epilepsy and Alzheimer Disease. *Front Neurol.* 2020 Jan 23;11:21. doi: 10.3389/fneur.2020.00021.
 57. Mueller SG, Laxer KD, Barakos J, Cheong I, Garcia P, Weiner MW. Widespread neocortical abnormalities in temporal lobe epilepsy with and without mesial sclerosis. *Neuroimage.* 2009 Jun;46(2):353-9. doi: 10.1016/j.neuroimage.2009.02.020.
 58. Butera A, D'Antoni S, Nicotera AG, Catania MV, Consoli C, et al. Neurodegeneration Biomarkers in Epilepsy: A Critical Review of Current Findings. *Life (Basel).* 2026 Feb 9;16(2):296. doi: 10.3390/life16020296.
 59. Madden DJ, Bennett IJ, Burzynska A, Potter GG, Chen NK, Song AW. Diffusion tensor imaging of cerebral white matter integrity in cognitive aging. *Biochim Biophys Acta.* 2012 Mar;1822(3):386-400. doi: 10.1016/j.bbadis.2011.08.003.
 60. Hatton SN, Huynh KH, Bonilha L, Abela E, Alhusaini S, et al. White matter abnormalities across different epilepsy syndromes in adults: an ENIGMA-Epilepsy study. *Brain.* 2020 Aug 1;143(8):2454-73. doi: 10.1093/brain/awaa200.
 61. Jiang M, Lee CL, Smith KL, Swann JW. Spine loss and other persistent alterations of hippocampal pyramidal cell dendrites in a model of early-onset epilepsy. *J Neurosci.* 1998 Oct 15;18(20):8356-68. doi: 10.1523/JNEUROSCI.18-20-08356.1998.
 62. Mohrmann L, Seebach J, Missler M, Rohlmann A. Distinct alterations in dendritic spine morphology in the absence of β -neurexins. *Int J Mol Sci.* 2024 Jan 20;25(2):1285. doi: 10.3390/ijms25021285.
 63. Jean G, Carton J, Haq K, Musto AE. The role of dendritic spines in epileptogenesis. *Front Cell Neurosci.* 2023 Aug 2;17:1173694. doi: 10.3389/fncel.2023.1173694.
 64. Buckmaster PS. Mossy Fiber Sprouting in the Dentate Gyrus. In: Noebels JL, Avoli M, Rogawski MA, Olsen RW, Delgado-Escueta AV, editors. *Jasper's Basic Mechanisms of the Epilepsies* [Internet]. 4th ed. Bethesda (MD): National Center for Biotechnology Information (US); 2012. PMID: 22787642.
 65. Sofroniew MV, Vinters HV. Astrocytes: biology and pathology. *Acta Neuropathol.* 2010 Jan;119(1):7-35. doi: 10.1007/s00401-009-0619-8.
 66. Edison P. Astroglial activation: Current concepts and future directions. *Alzheimers Dement.* 2024 Apr;20(4):3034-53. doi: 10.1002/alz.13678.

67. Yang G, Xu X, Gao W, Wang X, Zhao Y, Xu Y. Microglia-orchestrated neuroinflammation and synaptic remodeling: roles of pro-inflammatory cytokines and receptors in neurodegeneration. *Front Cell Neurosci.* 2025 Nov 10;19:1700692. doi: 10.3389/fncel.2025.1700692.
68. Suleymanova E, Karan A. The role of blood-brain barrier disruption in epilepsy: mechanisms and consequences. *Neurology Int.* 2026;18(1):1. doi: 10.3390/neurolint18010001.
69. Chen T, Dai Y, Hu C, Lin Z, Wang S, Yang J, et al. Cellular and molecular mechanisms of the blood-brain barrier dysfunction in neurodegenerative diseases. *Fluids Barriers CNS.* 2024 Jul 19;21(1):60. doi: 10.1186/s12987-024-00557-1.
70. Arias-Carrión O, Rodríguez de Ita J, Yu P. Innate immune signalling, neuroinflammation and network plasticity in temporal lobe epilepsy. *Front Pharmacol.* 2026 Feb 11;17:1770964. doi: 10.3389/fphar.2026.1770964.
71. Golarai G, Greenwood AC, Feeney DM, Connor JA. Physiological and structural evidence for hippocampal involvement in persistent seizure susceptibility after traumatic brain injury. *J Neurosci.* 2001 Nov 1;21(21):8523-37. doi: 10.1523/JNEUROSCI.21-21-08523.2001.
72. Fisher RS, Cross JH, French JA, Higurashi N, Hirsch E, et al. Operational classification of seizure types by the International League Against Epilepsy: Position Paper of the ILAE Commission for Classification and Terminology. *Epilepsia.* 2017 Apr;58(4):522-30. doi: 10.1111/epi.13670.
73. Auvin S, Arzimanoglou A, French J, Knupp KG, Lagae L, Trinka E, et al. Evolution of the European Medicines Agency clinical guidelines for epilepsy drug development between 2010 and 2025: A comparative analysis by the ILAE Task Force on Regulatory Affairs. *Epilepsia.* 2026 Feb 16. doi: 10.1002/epi.70152.
74. Mesraoua B, Brigo F, Lattanzi S, Abou-Khalil B, Al Hail H, Asadi-Pooya AA. Drug-resistant epilepsy: Definition, pathophysiology, and management. *J Neurol Sci.* 2023 Sep 15;452:120766. doi: 10.1016/j.jns.2023.120766.
75. Löscher W, White HS, Klein P. The complexity and challenges of developing effective epilepsy therapies: lessons to be learned from comparing cenobamate, carisbamate, and padsevonil. *CNS Drugs.* 2026 Jun;40(6):761-86. doi: 10.1007/s40263-026-01284-x.
76. Rogawski MA, Löscher W, Rho JM. Mechanisms of action of antiseizure drugs and the ketogenic diet. *Cold Spring Harb Perspect Med.* 2016 May 2;6(5):a022780. doi: 10.1101/cshperspect.a022780.
77. Curia G, Biagini G, Perucca E, Avoli M. Lacosamide: a new approach to target voltage-gated sodium currents in epileptic disorders. *CNS Drugs.* 2009;23(7):555-68. doi: 10.2165/00023210-200923070-00002.
78. Kim JJ, Gharpure A, Teng J, Zhuang Y, Howard RJ, Zhu S, et al. Shared structural mechanisms of general anaesthetics and benzodiazepines. *Nature.* 2020 Sep;585(7824):303-8. doi: 10.1038/s41586-020-2654-5.
79. Lynch BA, Lambeng N, Nocka K, Kensel-Hammes P, Bajjalieh SM, Matagne A, et al. The synaptic vesicle protein SV2A is the binding site for the antiepileptic drug levetiracetam. *Proc Natl Acad Sci U S A.* 2004 Jun 29;101(26):9861-6. doi: 10.1073/pnas.0308208101.
80. Krauss GL, Perucca E, Ben-Menachem E, Kwan P, Shih JJ, Squillacote D, et al. Perampamil, a selective, non-competitive α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor antagonist, as adjunctive therapy for refractory partial-onset seizures: interim results from phase III, extension study 307. *Epilepsia.* 2013 Jan;54(1):126-34. doi: 10.1111/j.1528-1167.2012.03648.x.
81. Kwan P, Brodie MJ. Early identification of refractory epilepsy. *N Engl J Med.* 2000 Feb 3;342(5):314-9. doi: 10.1056/NEJM200002033420503.
82. Sharifi-Rad J, Quispe C, Herrera-Bravo J, Martorell M, Sharopov F, et al. A Pharmacological perspective on plant-derived bioactive molecules for epilepsy. *Neurochem Res.* 2021 Sep;46(9):2205-25. doi: 10.1007/s11064-021-03376-0.
83. He X, Chen X, Yang Y, Xie Y, Liu Y. Medicinal plants for epileptic seizures: Phytoconstituents, pharmacology and mechanisms revisited. *J Ethnopharmacol.* 2024 Feb 10;320:117386. doi: 10.1016/j.jep.2023.117386.
84. Pradhan P, Jana K, Ghosh S, Debnath B, Rout SK, Rai VK, et al. Recent advances in bioactive flavonoids-based nanotherapeutics as promising neuroprotectants in epilepsy. *Curr Aging Sci.* 2025;18(3):211-43. doi: 10.2174/0118746098369369250119112935.
85. Alhamhoom Y, Kumar M R, C M, K K, Rahamathulla M, Albataineh H, et al. Green-synthesised *Matricaria chamomilla* silver nanoparticles enhance anticonvulsant and neuroprotective effects through GABAergic and antioxidant pathways in an acute seizure rat model. *RSC Adv.* 2026 May 5;16(25):23078-94. doi: 10.1039/d6ra01236a.
86. Hurley LL, Akinfiresoye L, Kalejaiye O, Tizabi Y. Anti-depressant effects of resveratrol in an animal model of depression. *Behav Brain Res.* 2014 Jul 15;268:1-7. doi: 10.1016/j.bbr.2014.03.052.
87. Waris A, Ullah A, Asim M, Ullah R, Rajdoula MR, et al. Phytotherapeutic options for the treatment of epilepsy: pharmacology, targets, and mechanism of action. *Front Pharmacol.* 2024 May 24;15:1403232. doi: 10.3389/fphar.2024.1403232.
88. Kou RW, Bai GY, Yang XY, Liu GS, He YQ, et al. Triterpenoids from the edible mushroom *Inonotus obliquus* attenuates cognitive impairment in vitro and in vivo. *Fitoterapia.* 2025 Oct;186:106865. doi: 10.1016/j.fitote.2025.106865.
89. Wang Y, Gu J, Wu J, Xu Y, Liu Y, et al. Natural products and health care functions of *Inonotus obliquus*. *Curr Issues Mol Biol.* 2025 Apr 10;47(4):269. doi: 10.3390/cimb47040269.
90. Bonetto V, Ferraresi A, Sampò S, Isidoro C. Fungal bioactive compounds as emerging therapeutic options for age-related neurodegenerative disorders. *Int J Mol Sci.* 2025 May 16;26(10):4800. doi: 10.3390/ijms26104800.