Neural Network Dysfunctions and Emerging Therapeutic Strategies in Epilepsy: A Comprehensive Review

Harshit Shringi and Muskan Tomar

ABSTRACT

Epilepsy is a persistent neurological condition defined by recurring, unprovoked seizures due to irregular neuronal coordination and impaired communication of neural circuits. Recent studies have indicated that the dysfunction of neural networks in epilepsy extends beyond hyperexcitability and includes maladaptive processes involving neuronal connectivity, glial signalling, and synaptic plasticity. The effects observed here are fundamentally driven by a cluster of pathophysiological changes involving oxidative stress, neuroinflammation, and mitochondrial derangements. Disruption of redox balance leads to increased production of reactive oxygen species that damage neuronal membranes while that trigger maladaptive alteration of neurotransmitters. Inflammatory molecules IL-1β, TNF-α, and NF-κB similarly deregulate synaptic efficacy and lead to excitotoxic cascades. This review aims to pull together our current understanding of molecular and cellular mechanisms that sustain dysfunction of neural networks and how molecular and cellular mechanisms can inform therapeutic interventions. Recent advances in antioxidant and anti-inflammatory drug development, nanocarrier-based biotechnology and drug delivery, gene therapy, or delivery of neuroprotective plant-based chemicals offer potentially promising directions, and show satisfactory evidence towards the goal of restoring network function. By establishing nexus for mechanistic understanding and translating that to implementation, our review will articulate a new potential for investigating precision-based, multi-targeted therapeutic interventions which can have impact upon seizure control and can maximise neuroprotection in epilepsy.

Keywords: Neural network dysfunction, Oxidativstress, Neuroinflammation, Synaptic plasticity, Nanocarrier-based therapy

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Additional material is published online only. To view please visit the journal online.

Cite this as: Shringi H and Tomar M. Neural Network Dysfunctions and Emerging Therapeutic Strategies in Epilepsy: A Comprehensive Review. Premier Journal of Science 2025;14:100192

DOI: https://doi.org/10.70389/PJS.100192

Peer Review

Received: 17 October 2025

Last revised: 17 November 2025

Accepted: 23 November 2025

Version accepted: 4

Published: 16 December 2025

Ethical approval: N/a

Consent: N/a

Funding: No external funding or financial support was received for the preparation of this manuscript. The work was conducted as part of academic research at the Acropolis Institute of Pharmaceutical Education and Research, Indore

Conflicts of interest: The authors declare that there are no

Introduction

About 50 million people worldwide suffer from epilepsy, a common neurological condition.[1] Recent developments have demonstrated that epilepsy is a complicated network failure involving several brain areas rather than just a localized illness.[2] Studies using functional neuroimaging have revealed changes in connection patterns that contribute to the epileptic state, such as hyperconnectivity in certain networks and hypoconnectivity in others. Different types of epilepsy are caused by these disturbances in network dynamics, which are also linked to treatment resistance and cognitive deficits.[3] Conventional anti-seizure drugs may not treat the underlying network dysfunctions, but they frequently target neuronal excitability.[4] These strategies include neuromodulation methods that seek to normalize abnormal network activity, such as transcranial magnetic stimulation and deep brain stimulation.[5] Furthermore, individualized therapy regimens that target certain network disorders are becoming possible because to developments in precision medicine that make use of genetic and neuroimaging data. Developing more focused and efficient treatment approaches requires an understanding of the brain network dysfunctions associated with epilepsy. People with epilepsy, especially those with drug-resistant forms, may benefit from better results if network neuroscience concepts are incorporated into therapeutic treatment. Clarifying the intricate network linkages in the epileptic brain and utilizing these discoveries to develop novel treatment approaches should be the main goals of future study.

Methods

Literature Search Strategy

A systematic literature search was conducted following PRISMA recommendations. PubMed, Scopus, Web of Science, ScienceDirect, and Google Scholar were searched from 2010 to 2025 to identify relevant studies on neural network dysfunction, molecular mechanisms, oxidative stress, neuroinflammation, synaptic plasticity, and emerging therapeutic strategies in epilepsy.

Eligibility Criteria

Inclusion Criteria

Studies were selected based on the following criteria:

- Published in peer-reviewed journals.
- Human studies, in vivo, in vitro, or high-quality mechanistic research.
- Articles focusing on neural network mechanisms, oxidative stress, neuroinflammation, glial activity, synaptic plasticity, and emerging epilepsy therapies.
- Review papers, original research, meta-analyses, and systematic reviews.
- English language publications.

Exclusion Criteria

- Case reports, conference abstracts, or non-peer-reviewed sources.
- Studies unrelated to epilepsy or lacking mechanistic or therapeutic relevance.
- Articles without accessible full text.
- Non-English publications.

Study Selection Process

The search retrieved ~215 studies. After removing duplicates, 176 studies remained. Titles and abstracts

conflicts of interest regarding the publication of this article. All authors have read and approved the final version of the manuscript

Author contribution: Harshit Shringi and Muskan Tomar contributed to conceptualization, literature search, and drafting of the manuscript and supervised the work, performed critical review, and provided intellectual input for manuscript refinement.

Guarantor: Muskan Tomar

Provenance and peer-review: Unsolicited and externally peer-reviewed

Data availability statement: N/a

were screened for relevance; 104 articles passed the first screening.Full-text evaluation resulted in 68 studies being included in the final review (Figure 1).

Two independent reviewers screened all papers to avoid bias. Disagreements were resolved through discussion.

Data Extraction and Evidence Synthesis

From each included study, the following information was extracted:

- Study design and model (clinical, animal, cellular)
- Mechanistic focus (oxidative stress, inflammation, mitochondrial dysfunction, etc.)
- Neural network findings
- Therapeutic interventions (antioxidants, phytochemicals, nanocarriers, gene therapies)
- Outcomes related to seizure activity, neuroprotection, synaptic changes, or network remodeling.

Because of the heterogeneity in methods and outcomes, a narrative synthesis approach was used instead of meta-analysis. Evidence was grouped by mechanistic themes and therapeutic strategies to build an integrated understanding of network dysfunction in epilepsy.

Mechanisms of Neural Network Dysfunction

Understanding this malfunction is essential to creating effective treatments for epilepsy, a complicated neurological illness marked by a breakdown of normal neural circuit balance. The primary characteristic of epilepsy is neural network dysfunction, which includes aberrant synchronization, neuronal hyperexcitability, glial activation, neuroinflammation, oxidative stress, and mitochondrial dysfunction. These factors all work together to cause seizures.[6] According to research, epileptic convulsions spread via dispersed networks such as the hippocampus, thalamocortical loops, and cortical-subcortical circuits rather of being localized in a single area of the brain.[7] Abnormalities at the network level impact behaviour, cognition, and response to therapy, especially in cases of drug-resistant epilepsy.[8] A major factor at the cellular level is an imbalance between excitation and inhibition; a dysregulation of glutamatergic excitatory and GABAergic inhibitory transmission causes hyperexcitable neurons and synchronous firing, which in turn causes seizures.[9] Glial cells, like as astrocytes and microglia, are important regulators of network failure. In addition to maintaining neuroinflammation, activated glial cells also increase neuronal excitability and network

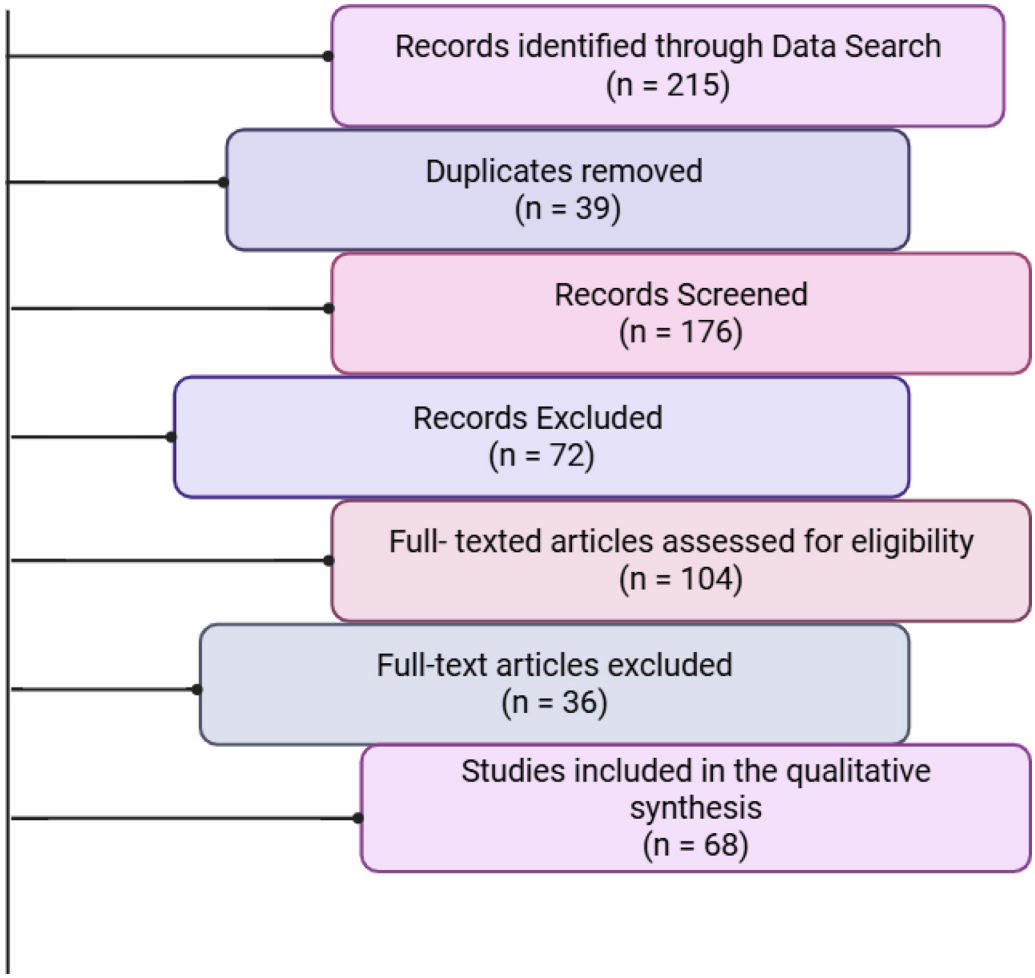

Fig 1 | PRISMA flow diagram showing the number of records identified (n = 215), screened (n = 176), excluded (n = 72), full-texts assessed (n = 104), full-texts excluded (n = 36), and final studies included in the qualitative synthesis (n = 68)

DOI: https://doi.org/10.70389/PJS.100192 | Premier Journal of Science 2025;14:100192

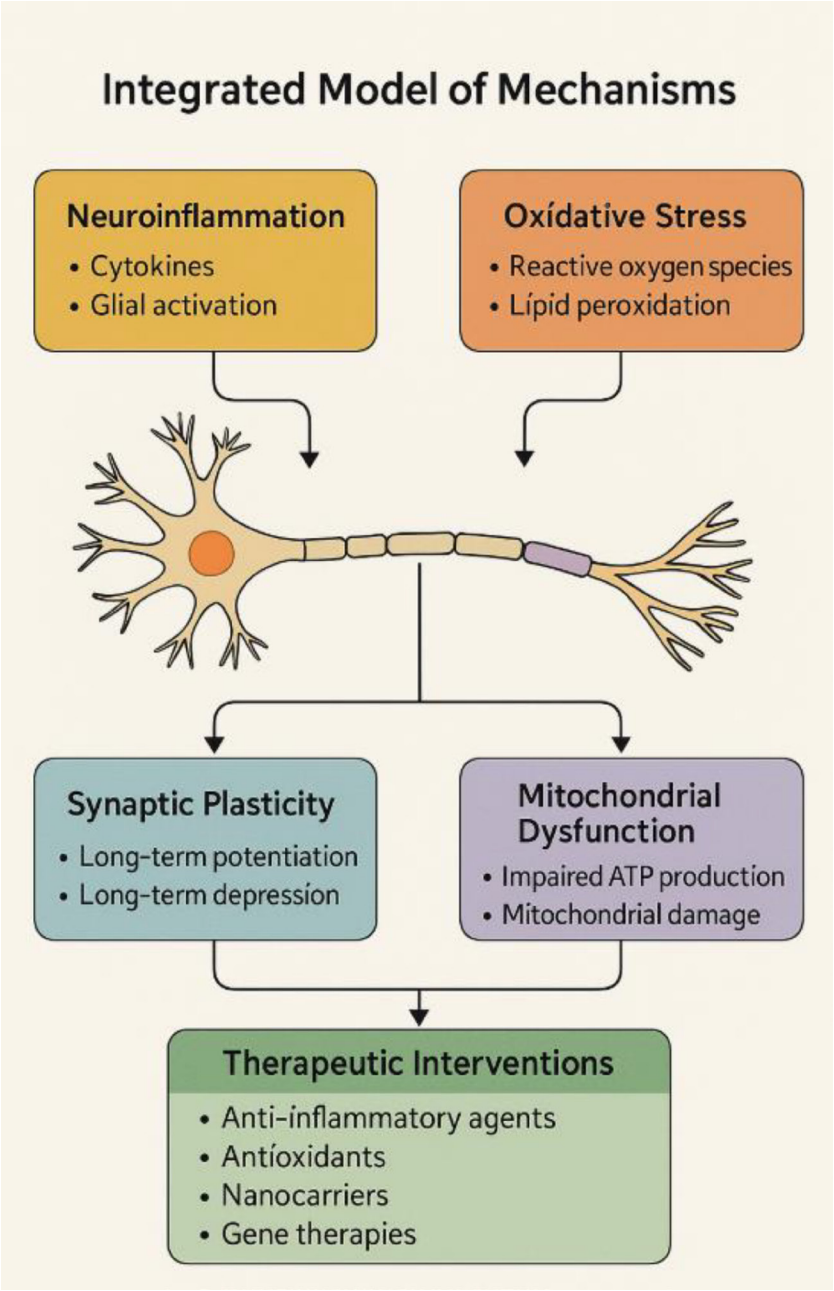

Fig 2 | Integrated model showing major mechanisms of neural network dysfunction in epilepsy and associated therapeutic targets

hypersynchrony by releasing pro-inflammatory cytokines and chemokines.[10] Other important factors include mitochondrial malfunction and oxidative stress. Reactive oxygen species (ROS) are produced during seizures, which damages neurons and kills cells. Mitochondrial dysfunction exacerbates network instability and epileptogenic by interfering with calcium homeostasis and energy metabolism. All things considered, neural network dysfunction in epilepsy is a complex process that includes disturbances at the cellular, synaptic, and network levels. Comprehending these systems serves as a basis for precision medicine tactics, neuromodulation techniques, and tailored medicines.[11,12] An integrated overview of these interacting mechanisms and their therapeutic targets is shown in Figure 2. Key preclinical mechanism–therapy–outcome relationships are summarised in Table 1.

Synaptic Plasticity and Network Remodelling

A key component of brain network dynamics and a key factor in epilepsy is synaptic plasticity. Changes in long-term depression (LTD) and long-term potentiation (LTP) brought on by epileptic episodes upset the regular equilibrium between synaptic strengthening and weakening. Both prolonged seizure susceptibility and network hyperexcitability are influenced by abnormal LTP/LTD. Both diffuse and localized brain areas, such as the cortex and hippocampus, undergo structural and functional network remodelling. Axonal sprouting, altered synaptic connection, and loss or hypertrophy of the dendritic spine are among the changes that influence network dynamics and seizure propagation. Patients with epilepsy frequently have memory loss, learning disabilities, and behavioural comorbidities as a result of these structural and functional changes, which have direct cognitive and behavioural effects. Developing tailored therapeutics to restore normal connectivity and cognitive function requires an understanding of the interaction between synaptic plasticity and network remodelling.[25]

Emerging Therapeutic Strategies in Epilepsy

Anti-seizure drugs have historically been the mainstay of epilepsy therapy; however, new therapeutic approaches have been made possible by a better knowledge of network breakdown, oxidative stress,

Table 1 | Preclinical mechanism–therapy–outcome mapping (evidence-graded)

Mechanism	Preclinical Therapy	Model	Outcome	Evidence Grade
Oxidative stress[13]	Resveratrol	Rat KA model	↓ ROS, ↑ mitochondrial protection	High
Neuroinflammation[14]	Minocycline	PTZ rat	↓ IL-1β, ↓ TNF-α	Moderate
Hyperexcitability[15]	NAC	Pilocarpine mice	↑ seizure threshold	High
Glial activation[16]	Curcumin	TLE rat	↓ microglial activation	Moderate
Mitochondrial dysfunction[17]	CoQ10	KA mice	↑ ATP, ↓ neuronal apoptosis	Low–Moderate
Synaptic remodeling[18]	Ginsenosides	PTZ mice	↓ LTP disruption	Low

neuroinflammation, and synaptic plasticity. These emerging molecular and network-directed approaches are summarised in Figure 3. These methods seek to lessen cognitive impairments, preserve neural circuits, and restore synaptic plasticity in addition to suppressing seizures.[26] Representative clinical phenotypes, dominant mechanisms, and corresponding therapies are outlined in Table 2.

Antioxidants & Anti-inflammatory Agents

Neuronal damage and seizure propagation are mostly caused by oxidative stress and persistent neuroinflammation. In preclinical models, antioxidants including resveratrol, N-acetylcysteine, and vitamin E have shown effectiveness by stabilizing mitochondrial activity and lowering reactive oxygen species (ROS). Anti-inflammatory drugs, such as IL-1 receptor antagonists and minocycline, reduce seizure thresholds, enhance cognitive function, and lessen glial-mediated neuroinflammation.[27] Recent antioxidant and neuroprotective compounds evaluated in epilepsy models are listed in Table 3.

Neuroprotective Phytochemicals

Curcumin, quercetin, and ginsenosides are examples of phytochemicals that provide multi-targeted neuroprotection through their modulation of oxidative stress, inflammatory pathways, and synaptic plasticity. According to preclinical research, these substances can improve mitochondrial function, lower seizure frequency, and balance LTP/LTD. Because of their promising neuroprotective properties and good safety profiles, they are being researched as supplemental treatments.[30]

Nanocarrier & Gene-Based Therapies

Drug delivery using nanocarriers and gene therapy techniques that target certain biochemical pathways or neural circuits are examples of advanced therapeutic methods. Nanocarriers enhance the targeted distribution

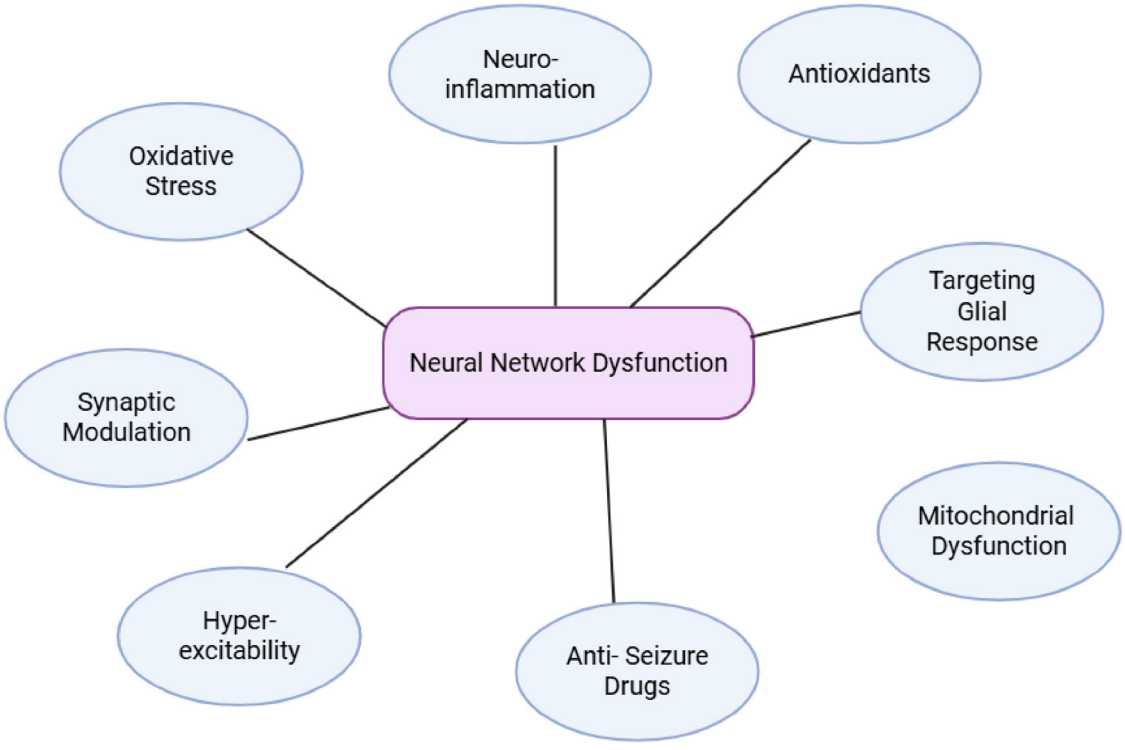

Fig 3 | Emerging therapeutic strategies targeting molecular and network-level dysfunction in epilepsy

Table 2 | Clinical phenotype–mechanism–therapy mapping (human studies)

Clinical Phenotype	Dominant Mechanism	Clinical Therapy	Clinical Evidence	Evidence Grade
Drug-resistant TLE[19]	Neuroinflammation	IL-1 inhibitors	Observed Human Studies	Moderate
Generalized epilepsy[20]	Hyperexcitability	Na^+/Ca^{2+} channel ASDs	Multiple RCTs	High
Post-traumatic epilepsy[21]	Oxidative stress	Vitamin E, antioxidants	Small Clinical Trials	Low–Moderate
Epilepsy with cognitive decline[22]	Network dysfunction	DBS, neuromodulation	Strong clinical data	High
Epilepsy with mitochondrial cytopathy[23]	Mitochondrial dysfunction	Antioxidant cocktails	Limited human evidence	Low

DOI: https://doi.org/10.70389/PJS.100192 | Premier Journal of Science 2025;14:100192

of antioxidants, phytochemicals, or anti-seizure medications, as well as their bioavailability and blood–brain barrier penetration. In order to treat refractory epilepsy precisely, gene therapy techniques such as CRISPR/Cas9-mediated ion channel regulation and viral vectors carrying neuroprotective genes seek to address network-level malfunction at the cellular level.[31]

Integration With Standards of Care, Limitations, and Translational Barriers

Current standards of care for epilepsy primarily rely on antiseizure drugs (ASDs), ketogenic diet therapy, neuromodulation approaches (VNS, DBS), and resective epilepsy surgery. While these established modalities remain essential, they often do not address the underlying pathophysiological mechanisms such as oxidative stress, chronic neuroinflammation, mitochondrial dysfunction, or network-level remodeling. Emerging therapies—including antioxidant agents, anti-inflammatory drugs, neuroprotective phytochemicals, nanocarrier-based formulations, and gene-targeted interventions—are therefore best conceptualized as adjunctive or precision-enhancing strategies, particularly in drug-resistant epilepsy.[32]

However, despite promising mechanistic rationale, several limitations restrict their clinical applicability. Antioxidants and phytochemicals exhibit poor bioavailability and limited human trial evidence. Anti-inflammatory therapies carry risks of systemic immune modulation. Nanocarriers face concerns regarding long-term biodistribution, scalability, and regulatory approval. Gene therapy poses challenges including off-target effects, vector-related toxicity, and extremely high treatment costs. Major translational barriers also exist. Preclinical epilepsy models fail to fully mirror human network dynamics, limiting the predictive value of laboratory findings. Safety and efficacy data for chronic use of nanoparticles, immunomodulators, and gene-based therapies remain insufficient. Manufacturing standardization and regulatory pathways for advanced biologics and nanotechnologies are complex and costly. Additionally, accessibility is a significant challenge, especially in low- and middle-income regions where treatment gaps persist. Overall, while these emerging approaches hold substantial promise, large-scale clinical trials, long-term safety studies, and regulatory harmonization are essential before they can be integrated into mainstream epilepsy care. An integrated view linking mechanisms, therapies, and clinical subtypes is provided in Table 4.

Table 3 | Recent antioxidant & neuroprotective compounds

Compound	Mechanism of Action	Observed Effects in Epilepsy Models
Resveratrol[28]	Antioxidant, mitochondrial stabilizer	Reduced ROS, improved synaptic plasticity
Curcumin[15]	Anti-inflammatory, antioxidant	Decreased neuroinflammation, reduced seizure frequency
Quercetin[29]	Neuroprotective flavonoid	Improved mitochondrial function, decreased neuronal apoptosis
N-acetylcysteine (NAC)[16]	ROS scavenger, glutathione precursor	Lowered oxidative stress, improved seizure threshold

Conclusion and Future Directions

It is becoming more widely acknowledged that epilepsy is a condition of neural network malfunction, with abnormal synaptic plasticity, glial cell activation, and neuronal synchronization. Cognitive deficits and behavioural comorbidities are among the ictal and interictal signs that are caused by these pathophysiological alterations . Antiepileptic medications (AEDs) are readily available, yet there are still large treatment gaps worldwide, especially in low- and middle-income nations. Delays in diagnosis, poor treatment optimization, and restricted access to healthcare are the main causes of these disparities. Furthermore, the underlying network dysfunctions and related cognitive deficiencies are frequently ignored by modern AEDs, which exclusively target seizure management. New developments in network-based methods, such as the use of graph theory and neuroimaging techniques, provide encouraging paths for comprehending and addressing the damaged brain circuits in epilepsy. Furthermore, new treatment approaches that target neuroinflammation, mitochondrial function, and oxidative stress management seek to offer neuroprotective benefits outside of the realm of conventional AEDs. The creation of precision medicine strategies that combine network-level insights with customized treatment regimens should be the main focus of future research. In order to restore normal network function and enhance long-term results for people with epilepsy, this involves investigating new pharmacological treatments, gene-based therapies, and neuromodulation approaches. In conclusion, filling the existing therapy gaps and developing therapeutic approaches that focus on the underlying pathophysiology of the

Table 4 | Integrated mechanism → therapy → phenotype summary

Mechanism	Best-Supported Therapy	Most Affected Clinical Subtype	Level of Evidence
Oxidative stress[24]	Antioxidants (NAC, Resveratrol)	Focal & post-traumatic epilepsy	High (preclinical), Low (clinical)
Neuroinflammation	IL-1 blockers, Minocycline	TLE with HS	Moderate
Hyperexcitability	ASDs (Na^+/Ca^{2+}/GABA)	Generalized epilepsy	High
Glial Activation	Curcumin, flavonoids	TLE	Moderate
Mitochondrial dysfunction	CoQ10, L-carnitine	Metabolic Epilepsy	Low
Synaptic Plasticity Defects	Phytochemicals, neuromodulation	Cognitive Impairment Epilepsy	Low–Moderate

condition require a thorough knowledge of the neural network dysfunctions in epilepsy.

List of Abbreviations

AEDs – Antiepileptic Drugs
ASDs – Antiseizure Drugs
ATP – Adenosine Triphosphate
BBB – Blood–Brain Barrier
CA – Cornu Ammonis (Hippocampal Region)
CNS – Central Nervous System
COX – Cyclooxygenase
CRISPR – Clustered Regularly Interspaced Short Palindromic Repeats
CoQ10 – Coenzyme Q10
DBS – Deep Brain Stimulation
DNA – Deoxyribonucleic Acid
EEG – Electroencephalography
EGCG – Epigallocatechin Gallate
FDA – Food and Drug Administration
GABA – Gamma-Aminobutyric Acid
GLUT – Glucose Transporter
HS – Hippocampal Sclerosis
IL-1β – Interleukin-1 Beta
IL-6 – Interleukin-6
ILAE – International League Against Epilepsy
KA – Kainic Acid
LTP – Long-Term Potentiation
LTD – Long-Term Depression
MMPs – Matrix Metalloproteinases
MRI – Magnetic Resonance Imaging
mRNA – Messenger Ribonucleic Acid
mtDNA – Mitochondrial DNA
NAC – N-Acetylcysteine
NF-κB – Nuclear Factor Kappa B
NMDAR – N-Methyl-D-Aspartate Receptor
PRISMA – Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PTZ – Pentylenetetrazol
RCTs – Randomized Controlled Trials
ROS – Reactive Oxygen Species
SOD – Superoxide Dismutase
TLE – Temporal Lobe Epilepsy
TNF-α – Tumor Necrosis Factor Alpha
VNS – Vagus Nerve Stimulation
WHO – World Health Organization

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