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THE EFFECT OF PROBIOTIC BACTERIA LACTOBACILLUS SPP. AND BIFIDOBACTERIUM SPP. AS A NOVEL EFFECTIVE THERAPY FOR SEIZURES IN EPILEPSY: A SYSTEMATIC REVIEW OF PRECLINICAL STUDY DESIGNS

Rince Restiviona[1], Cimi Ilmiawati[2], Mayetti Akmal[3], Yuliarni Syafrita[4]*
[1]Doctoral Program in Biomedical Science, Faculty of Medicine, Universitas Andalas, Jln Perintis Kemerdekaan No 94, Limau Manis, Pauh, Padang, Sumatera Barat 25166, Indonesia
[2]Department of Pharmacology, Faculty of Medicine, Universitas Andalas, Jln Perintis Kemerdekaan No 94, Limau Manis, Pauh, Padang, Sumatera Barat 25166, Indonesia
[3]Department of Pediatrics, Faculty of Medicine, Universitas Andalas, Jln Perintis Kemerdekaan No 94, Limau Manis, Pauh, Padang, Sumatera Barat 25166, Indonesia
[4]Department of Neurology, Faculty of Medicine, Universitas Andalas, Jln Perintis Kemerdekaan No 94, Limau Manis, Pauh, Padang, Sumatera Barat 25166, Indonesia
*yuliarni@med.unand.ac.id

ABSTRACT
Epilepsy is a chronic neurological disorder characterized by recurrent seizures due to abnormal electrical activity in the brain. The seizure mechanism involves neurotransmitter imbalance, oxidative stress, and neuroinflammation. Recent studies highlight the role of the gut–brain axis, emphasizing probiotics such as Lactobacillus spp. and Bifidobacterium spp., which potentially stabilize the nervous system through microbiota modulation and anti-inflammatory effects. This review aims to systematically assess preclinical evidence on the efficacy of Lactobacillus spp. and Bifidobacterium spp. as adjunctive therapies to reduce seizures in epilepsy through molecular and gut–brain axis mechanisms. This systematic review followed PRISMA guidelines, with literature searches performed in Google Scholar, PubMed, Taylor & Francis, and ScienceDirect, including publications from 2015 to 2025 (1576 articles to 13 articles), and inclusion criteria based on the PICOS framework. Risk of bias was assessed using Sycle's risk of bias tool. A total of 13 in vivo preclinical stu
dies of Lactobacillus spp. and Bifidobacterium spp. reported significant effectiveness in reducing seizure symptoms and regulating excitatory–inhibitory neurotransmitter balance in rat models of induced epilepsy. Probiotics have potential as effective alternative therapies in modulating seizure reduction and maintaining neurotransmitter balance during epilepsy. They may be developed in the future as non-pharmacological therapeutics based on microbiota.

Keywords: bifidobacterium sp.; epilepsy; lactobacillus sp.; neurotransmitters; seizure

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INTRODUCTION

Epilepsy is one of the most common chronic neurological disorders, characterized by abnormal electrical activity in the brain that triggers recurrent and unpredictable seizure episodes. Epileptic seizures may manifest as brief lapses in consciousness, localized or generalized muscle contractions, or complete loss of body control (Chen et.al., 2023). It not only diminishes the patient's quality of life but also impacts cognitive, psychological, and social domains (Mula and Sander, 2016). Children and the elderly are among the most vulnerable populations, with uncontrolled epilepsy often leading to serious complications such as developmental delays, intellectual disabilities, and even sudden unexpected death in epilepsy (SUDEP) (Suller et al., 2022; Pathak et al., 2025). Although antiseizure medications (ASMs) remain the primary epilepsy management and successfully control seizures in about two-thirds of patients, nearly 30% of individuals with newly diagnosed epilepsy fail to achieve seizure remission with pharmacological therapy and are classified as having drug-resistant epilepsy (DRE) (Chen et.al., 2023). Therefore, there is a need for safer and more effective therapeutic approaches.

Seizures in epilepsy are typically caused by an imbalance between excitatory systems (stimulate neuronal activity) and inhibitory systems (suppress neuronal activity) in the brain (Akyuz et al., 2021). It can result from genetic factors, brain injury, infection, tumours, or metabolic disorders (Ninds, 2025). At the molecular level, epileptic seizures are associated with dysregulation of neurotransmitters such as Glutamate (excitatory) and gamma-aminobutyric acid/GABA (inhibitory), oxidative stress, and activation of inflammatory pathways within the central nervous system. These processes increase neuronal excitability and lower the seizure threshold (Li et al., 2023). Furthermore, the interaction between the central nervous system and gut microbiota is increasingly recognized as an important mechanism in the pathophysiology of epilepsy. Communication between the gut and brain through the microbiota–gut–brain axis has become a focus of modern research, exploring non-pharmacological therapeutic approaches to epilepsy (Ding et al., 2021).

The use of probiotics as a complementary therapy in various neurological disorders, including epilepsy, has begun to show potential as a therapy. Probiotics are live microorganisms that confer health benefits to the host when consumed in adequate amounts. Prebiotics' function is to modulate gut microbiota, strengthen intestinal barrier integrity, reduce systemic permeability, and reduce production of inflammatory mediators that contribute to nervous system dysfunction (Bian and Shao, 2024; Wang et al., 2022). Experimental studies in animal models of epilepsy have shown that probiotic administration can reduce the frequency and severity of seizures by improving gut metabolite profiles (e.g., short-chain fatty acids), modulating immune responses, and enhancing brain antioxidant enzyme activity. These findings support the hypothesis that gut microbiota plays a crucial role in neuroinflammation and neuronal excitability, which are key contributors to epileptic seizures (Bagheri et al., 2019).

The most commonly used in prebiotic studies in the context of neurological disorders, including epilepsy, are Lactobacillus spp. and Bifidobacterium spp. These bacteria are known for their ability to maintain gut microbiota homeostasis and produce neurotransmitters such as GABA and serotonin (Peng et al., 2018; Strandwitz, 2018). Lactobacillus sp. has been reported to enhance GABA-related gene expression and suppress proinflammatory cytokines such as IL-6 and TNF-α, both of which are implicated in neuroinflammation associated with epilepsy (Eor et al., 2021). Meanwhile, Bifidobacterium sp. exhibits immunomodulatory and antioxidant properties that help reduce oxidative stress and maintain the integrity of the blood-brain barrier (BBB), which is often disrupted during epileptic states (Zubareva et al., 2023). The combination of these two probiotics may synergistically enhance neuroprotective effects and reduce seizure incidence in rat models of epilepsy induced by kainic acid or pilocarpine.

It is important to conduct scientific exploration into the potential of Lactobacillus spp. and Bifidobacterium spp. as innovative therapies for epilepsy, particularly in addressing drug-resistant seizures. A systematic review of preclinical study designs can provide a strong scientific foundation for evaluating the efficacy, mechanisms of action, and translational potential of these probiotics, especially Lactobacillus spp. and Bifidobacterium spp., in therapeutic approaches for humans. This review aims to systematically assess preclinical evidence on the efficacy of Lactobacillus spp. and Bifidobacterium spp. as adjunctive therapies to reduce seizures in epilepsy through molecular and gut–brain axis mechanisms.

METHOD
To ensure transparent and standardized reporting, this systematic review was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines, and the selection process was illustrated using the PRISMA flow diagram (Page et al., 2020).

Eligibility criteria

Studies were eligible if the following criteria were determined using the PICOS framework (Population or problem, Intervention, Comparison, Outcomes), as summarized in the Table.1 (Methley et al., 2014; Amir and Janati, 2020). Additional inclusion criteria included: preclinical studies, written in English, available in full text.

Table 1.
PICOS Criteria

Criteria	Inclusion
Problem	Epilepsy or recurrent seizure
Intervention	Lactobacillus spp. and/or Bifidobacterium spp. as primary or adjuvant therapy
Comparison	Any control group used by the included studies
Outcome	Type of neurotransmitter (inhibitory/excitatory), Onset, duration, type and severity of seizures

The exclusion criteria were as follows: (i) articles outside of in vivo study design, (ii) meta-analyses, systematic reviews, and literature reviews, (iii) articles not available in full text, and (iv) articles not focusing on *Lactobacillus spp., Bifidobacterium spp.,* seizures, or epilepsy.

Information sources

Google Scholar, PubMed, Taylor & Francis, and ScienceDirect were searched for primary studies between 2015 and 2025.

Article search

The article search was conducted using the following keywords: (*Lactobacillus* AND *Bifidobacterium* AND seizure AND epilepsy) across four health-related databases: Google Scholar, PubMed, Taylor & Francis, and ScienceDirect. The journal articles reviewed were limited to preclinical studies, including in vivo research, published between 2015 and May 6, 2025.

Study selection

Titles and abstracts were screened independently by the author (RR) and the co-author (CI) for potential inclusion according to eligibility criteria. For included studies, duplicate independent screening of the whole article was conducted by the primary and secondary reviewers (RR and CI), and any disagreements regarding inclusion were resolved through discussion, including with second and third co-authors (MA and YS) if needed.

Data collection process

Data were then extracted into a standard form, including title, abstract, methodology, and duplication. Duplicate data extraction was conducted independently by RR and CI, and any discrepancies were resolved through discussion, including with another author if required (AK and YS). Only published data were collected, with no additional data sought from study authors. Outcome data were (1) author and year of study, (2) characteristic sample, (3) kind of epilepsy induction, (4) study objectives, (5) molecular target, (6) type of seizure, and (7) prebiotics strain.

Risk of bias and quality of studies

The author and co-authors examined studies and outcomes for methodological rigour independently – using the syrcle's bias tool for assessing risk of bias for clinical study. Any discrepancies were resolved through discussion, including with another author if required. Each domain is assessed using three classifications: 'low risk,' 'high risk,' or 'unclear risk,' based on the signaling questions and the information available from the article.

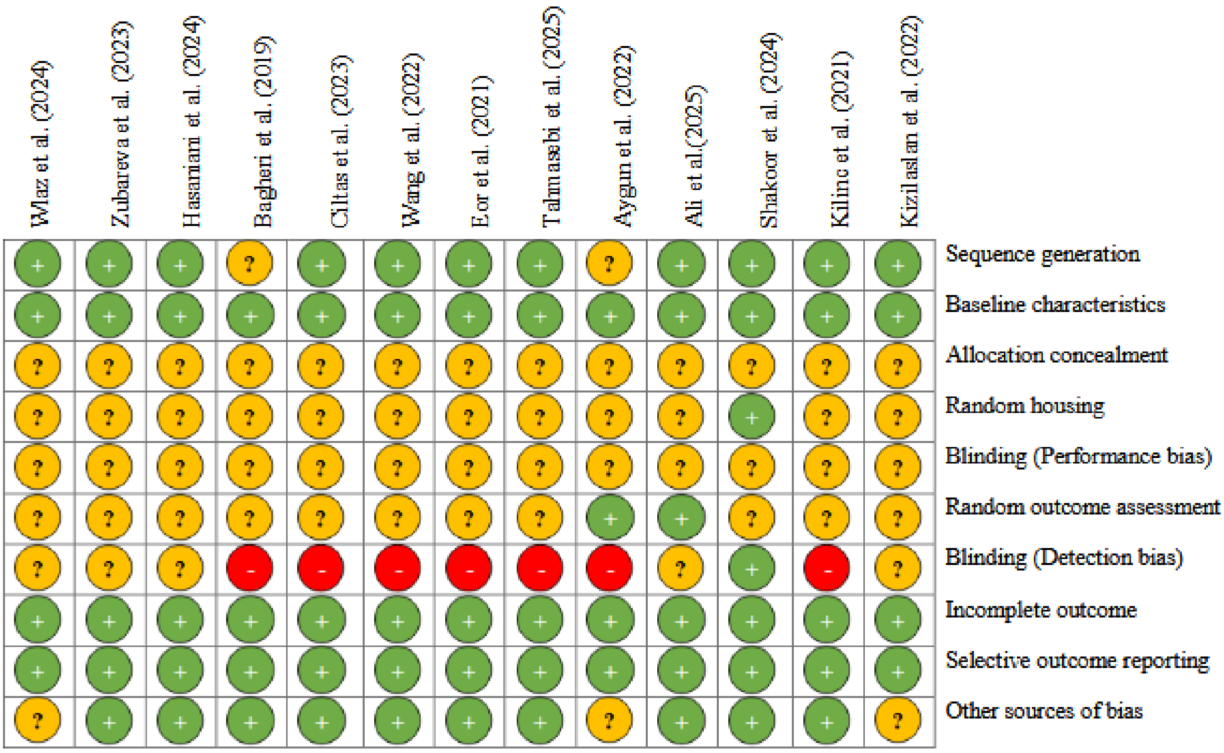

Figure 1. SYRCLE's Risk of Bias (RoB) Tool

RESULT

This systematic review identified 13 eligible studies out of 1,576 initial records. The included articles were selected based on the predefined inclusion criteria and subsequently extracted according to the data extraction framework. The valid article selection process is illustrated in Figure 1.

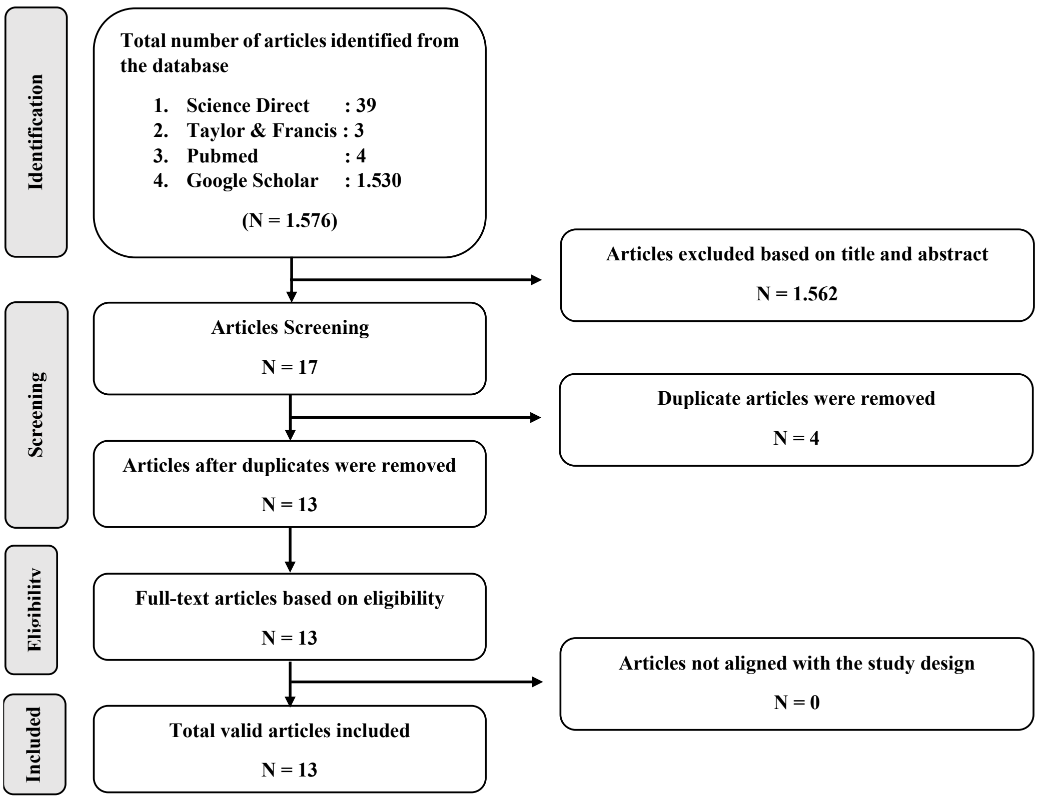

Figure 2. PRISMA diagram

Table 2.
Extraction Data Result

Authors	Sample	Kind of epilepsy induction	Study objective	Type of Neurotransmitter	Type of seizure Assignment	Probiotic strain	
						Lactobacillus sp.	*Bifidobacterium* sp.
Zubareva *et al*., 2023	Male Wistar rats (7 weeks) were randomly assigned to four groups (n=16)	LiCl–*pilocarpine (i.p.)*	To investigate the effect of *Bifidobacterium longum* probiotic administration on seizures in rats with epilepsy.	NR	NR	-	*Bifidobacterium longum*
Hasaniani *et al*., 2024	Male Wistar rats (5-6 weeks) were randomly assigned to five groups (n=8)	*Cuprizone (p.o.)*	To evaluate the effect of Lactobacillus casei and Bifidobacterium breve administration on brain demyelination in a pre-epileptic rat model.	NR	NR	*Lactobacillus casei 10711*	*Bifidobacterium breve 1367*
Wlaz *et al*., 2023[32]	Albino Swiss mice (5-6 weeks) were randomly allocated into five groups (n=20)	*electroshock* dan *Pentylenetetrazol (i.v.)*	To assess the effect of single-strain Lactobacillus helveticus administration on seizures in rats with epilepsy.	NR	NR	*Lactobacillus helveticus R0052*	-
Bagheri *et al*., 2019[11]	Adult male Wistar rats were randomly assigned to 5 groups (n=8)	*Pentylenetetrazol (i.p.)*	To investigate the effect of a mixed probiotic formulation containing Lactobacillus spp. and Bifidobacterium spp. on seizures in epileptic rats.	Inhibitory (GABA)	Scoring of seizure	*Lactobacillus Rhamnosus* *Lactobacillus reuteri*	*Bifidobacterium infantis*
Ciltas *et al*., 2023[33]	Adult male Wistar rats were randomly assigned to 4 groups (n=6)	*Pentylenetetrazol (i.p.)*	To evaluate the effect of a mixed probiotic containing Lactobacillus spp. and Bifidobacterium spp. on seizures in rats with epilepsy.	Inhibitory (GABA) and Excitatory (Glutamate)	Scoring and onset of seizure.	*Lactobacillus acidophilus* *Lactobacillus casei* *Lactobacillus plantarum* *Lactobacillus salivarius* *Lactobacillus rhamnosus* *Lactobacillus bulgaricus* *Lactobacillus paracasei*	*Bifidobacterium lactis* *Bifidobacterium breve* *Bifidobacterium longum* *Bifidobacterium bifidum*
Wang *et al*., 2022	Adult male Wistar rats	*Kainic acid (i.a)*	To evaluate the effect of gut	NR	Score, duration	*Lactobacillus* sp.	*Bifidobacterium* sp.

Authors	Sample	Kind of epilepsy induction	Study objective	Type of Neurotransmitter	Type of seizure Assignment	Probiotic strain	
						Lactobacillus sp.	*Bifidobacterium* sp.
	were randomly allocated into five groups		dysbiosis induction on seizures in rats with epilepsy.		, and frequency of seizure.		
Eor *et al*., 2021	Male mice (3 weeks) were randomly allocated into eight groups (n=5)	*Pentylenetetrazol (i.p.)*	To investigate the effect of single-strain Lactobacillus fermentum supplementation combined with a ketogenic diet on seizures in epileptic rats.	Inhibitory (GABA)	Score, onset, and frequency of seizure	*Lactobacillus fermentum MSK 408*	-
Tahmasebi *et al*., 2025	Adult male Wistar rats were randomly allocated into four groups (n=10)	*Pentylenetetrazol (i.p.)*	To evaluate the effect of Lactobacillus spp. and Bifidobacterium spp. Administration of seizures in epileptic rats, as assessed through inflammatory response and seizure activity.	NR	Score and duration of seizure	*Lactobacillus reuteri*	*Bifidobacterium longum* *Bifidobacterium lactis*
Aygun *et al*., 2022	Adult male Wistar rats WAG/Rij were randomly assigned to three groups (n=7)	Tikus Transgenik WAG/Rij	To evaluate the effect of Lactobacillus spp. and Bifidobacterium spp. Administration on seizure activity in transgenic epileptic rats, with a focus on anxiety and depression-like behavioral responses.	NR	NR	*Lactobacillus plantarum* *Lactobacillus acidophilus* *Lactobacillus delbrueckii subsp. Bulgaricus* *Lactobacillus casei*	*Bifidobacterium longum* *Bifidobacterium breve* *Bifidobacterium infantis*
Ali *et al*., 2025	Male mice BALB/c were randomly assigned to six groups (n=6-8)	*Pentylenetetrazol (i.p.)*	To evaluate the effect of Lactobacillus spp. and Bifidobacterium spp. Administration of seizures in an experimental rat model of epilepsy.	NR	Scoring of seizure	*Lactobacillus* sp.	*Bifidobacterium* sp.
Shakoor *et al*., 2024	Male mice BALB/C were randomly assigned to	*Pentylenetetrazol (i.p.)*	To investigate the effect of Lactobacillus spp. and Bifidobacterium	NR	Scoring of seizure	*Lactobacillus* sp.	*Bifidobacterium* sp.

Authors	Sample	Kind of epilepsy induction	Study objective	Type of Neurotransmitter	Type of seizure Assignment	Probiotic strain	
						Lactobacillus sp.	*Bifidobacterium* sp.
	six groups (n=4-6)		spp. Administration of seizures in a rat model of epilepsy.				
Kilinc *et al*., 2021	Adult male Wistar rats (4 weeks) were randomly allocated into four groups (n=12)	*Pentylenetetrazol (i.p.)*	To evaluate the effect of Lactobacillus spp. and Bifidobacterium spp. Administration of seizures in epileptic rats, as assessed through inflammatory response, antioxidant activity, and seizure parameters.	NR	Score, onset, and duration of seizure.	*Lactobacillus Acidophilus Lactobacillus casei Lactobacillus plantarum Lactobacillus salivarius Lactobacillus rhamnosus Lactobacillus bulgaricus Lactobacillus paracasei*	*Bifidobacterium lactis Bifidobacterium breve Bifidobacterium longum Bifidobacterium bifidum*
Kizilaslan *et al*., 2022	Adult male Wistar rats were randomly allocated into three groups (n=7)	*Penicillin (i.cort.)*	To investigate the effect of Lactobacillus spp. and Bifidobacterium spp. Administration of seizures in an experimental rat model of epilepsy.	NR	NR	*Lactobacillus plantarum Lactobacillus acidophilus Lactobacillus delbrueckii subsp. Bulgaricus Lactobacillus casei*	*Bifdobacterium longum Bifdobacterium breve Bifdobacterium infantis*

Note : NR = Not Reported

Table 3.
Extraction Data Result (Outcome)

Authors	Outcome
Zubareva *et al*., 2023	*Bifidobacterium longum* was found to enhance anti-inflammatory and neuroprotective factors while downregulating pro-inflammatory mediators in the temporal cortex of epileptic rat models. Behaviourally, this probiotic reduced the occurrence of spontaneous seizures and improved seizure-related symptoms.
Hasaniani *et al*., 2024	Epilepsy comorbid with demyelination was attenuated by *Bifidobacterium breve* and *Lactobacillus casei*, which enhanced antioxidant capacity and improved cognitive performance, indicating a relevant link between oxidative stress, cognition, and epilepsy.
Wlaz *et al*., 2023	Supplementation with *Lactobacillus helveticus* R0052 increased seizure thresholds (notably in 6 Hz and PTZ-clonic models) and enhanced short-chain fatty acid (SCFA) production, suggesting modulation of the gut–brain axis. The probiotic also elevated serum valproate activity without affecting motor function or anxiety-related behaviour.
Bagheri *et al*., 2019	Administration of probiotics (*Lactobacillus rhamnosus*, *L. reuteri*, *Bifidobacterium infantis*) reduced seizure scores, prevented full kindling, elevated GABA levels, and improved spatial memory. Oxidative stress markers also decreased, particularly when probiotics were administered during the kindling process.
Ciltas *et al*., 2023	Probiotic administration delayed seizure onset, increased hippocampal GABA levels, and enhanced total antioxidant status. Glutamate levels were also modulated, contributing to reduced seizure manifestations in epileptic rats.
Wang *et al*., 2022	In a *status epilepticus* model, probiotics decreased seizure frequency, duration, and severity, while improving spatial memory. Probiotics downregulated pro-inflammatory cytokines and oxidative stress markers, indicating strong antioxidant and anti-inflammatory effects that contributed to epilepsy improvement.

Authors	Outcome
Eor *et al.*, 2021	Synbiotic supplementation (*Lactobacillus fermentum* MSK 408 + GOS), with or without a ketogenic diet, reduced seizure severity, increased GABA levels, decreased glutamate, and improved SCFA profiles. Additionally, seizure scores decreased, onset was delayed, and frequency was reduced, suggesting protective potential without interfering with ketogenic diet efficacy.
Tahmasebi *et al.*, 2025	Probiotic supplementation (*L. reuteri*, *B. longum*, *B. lactis*) administered before and during seizures in epileptic rats delayed seizure onset, downregulated pro-inflammatory factors, and upregulated anti-inflammatory mediators. Probiotics also protected hippocampal tissue from damage, demonstrating anti-inflammatory and neuroprotective properties.
Aygun *et al.*, 2022	A combination of *Lactobacillus* and *Bifidobacterium* spp. reduced the number and duration of spike-wave discharges (SWDs) in an epileptic rat model. Probiotics improved anxiety- and depression-related behaviours, enhanced anti-inflammatory factors, and downregulated pro-inflammatory mediators in the brain, supporting their neurotrophic and anti-inflammatory modulatory roles.
Ali *et al.*, 2025	Combined administration of *Lactobacillus* and *Bifidobacterium* spp. with pregabalin exerted potent anticonvulsant effects in epileptic rat models by reducing seizure scores and EEG spike frequency. Molecularly, this combination enhanced antioxidant enzyme activity, lowered oxidative stress biomarkers, and mitigated inflammation and neuronal apoptosis in hippocampal regions. Behaviourally, cognitive impairment, anxiety, and depression were also ameliorated following probiotic administration.
Shakoor *et al.*, 2024	Long-term supplementation of *Lactobacillus* and *Bifidobacterium* spp. combined with brivaracetam reduced seizure progression, increased seizure thresholds, and decreased EEG spike activity. Improvements in anxiety and depressive behaviours were also observed. At the molecular level, this intervention restored redox balance by reducing oxidative stress markers and preserving neuronal morphology from degeneration.
Kilinc *et al.*, 2021	Administration of a probiotic mixture (*Bifidobacterium* and *Lactobacillus* spp.) significantly delayed seizure onset (both myoclonic and tonic–clonic) and reduced tonic–clonic seizure duration in an acute PTZ-induced epilepsy model. Molecular analyses revealed decreased pro-inflammatory factors in plasma and brain tissue, indicating reduced inflammation and oxidative stress.
Kizilaslan *et al.*, 2022	Probiotic supplementation containing *Lactobacillus* and *Bifidobacterium* spp. in a focal seizure model induced by intracortical penicillin injection significantly increased seizure latency and reduced ECoG spike frequency. Molecularly, pro-inflammatory and oxidative stress markers in brain tissue were downregulated, supporting the anti-inflammatory and neuroprotective effects of probiotics against focal seizures.

Table 4.
GABA and Glutamate Levels in Epileptic Rats Administered Probiotics

Authors	GABA level		Glutamate level		p Value	
	Control (+)	Probiotic	Control (+)	Probiotic	GABA	Glutamate
Bagheri *et al.*, 2019	<0,7 ng/g/g	>0,8 ng/g	NR	NR	<0,01 (significant)	NR
Ciltas *et al.*, 2023	<4 Nm/g	>5 Nm/g	>7 Nm/g	<7 Nm/g	<0,05 (significant)	>0,05 (not significant)
Eor *et al.*, 2021	<50 pg/mL	> 70 pg/mL	> 20 M/L	<20 M/L	<0,05 (significant)	<0,05 (significant)

DISCUSSION

Pathophysiology and Pathogenesis of Seizures in Epilepsy

Epilepsy is a chronic neurological disorder characterized by the brain's recurrent ability to generate abnormal electrical discharges, leading to spontaneous seizures. This condition not only involves electrical disturbances in neurons but also reflects widespread structural and molecular reorganization within the central nervous system. The pathophysiological mechanism of epilepsy begins with epileptogenesis, which refers to the transformation of normal brain tissue into epileptogenic tissue (Pitkänen et al., 2015). This process is typically triggered by an initial brain insult such as head trauma, infection, stroke, cortical malformations, or genetic abnormalities, which leads to excitatory activity due to increased glutamate release, blood–brain barrier dysfunction, immune activation, and oxidative stress (Ninds, 2025). During the latent phase after initial brain injury, there are alterations in gene and synaptic protein expression, loss of GABAergic inhibitory neurons, and neural circuit reorganization, such as mossy fiber sprouting in the hippocampus, that progressively enhance brain excitability. These alterations eventually result in neural networks capable of producing synchronized electrical activity and spontaneous hyperexcitability (Hunt et al., 2011).

When a seizure occurs, abnormal electrical activity spreads across neuronal tissues through both cortical and subcortical pathways. The clinical manifestations of seizures vary depending on the location and extent of the abnormal activity. In focal seizures, symptoms may include involuntary muscle movements, unusual sensations, or partial alterations in consciousness. In contrast, generalized seizures such as tonic-clonic seizures are characterized by loss of consciousness, widespread muscle contractions, and are often followed by a postictal phase marked by confusion, fatigue, or temporary paralysis (Todd's paralysis) (Ighodaro et al., 2025). Some patients also experience kinetic responses preceding seizures, such as visual, olfactory, or emotional sensations that mark the onset of epileptiform activity. In children, seizure variants may include absence seizures or infantile spasms, each characterized by distinct electrical activity patterns and behavioral manifestations (Giordano et al., 2020).

In addition to the clinical features, there exists a complex and interconnected molecular mechanism that underlies the development and recurrence of seizures in the pathogenesis of epilepsy. A key component of this mechanism is ion channel dysfunction, particularly involving sodium, potassium, and calcium channels, which play a critical role in synaptic transmission and action potential propagation. Mutations in the SCN1A, SCN2A, and SCN8A genes, which encode voltage-gated sodium channels, can lead to loss of GABAergic interneuron function, resulting in delayed neuronal repolarization and prolonged electrical activity (Menezes et al., 2020). T-type calcium channels (e.g., CACNA1H) are also implicated in regulating burst firing in the thalamus, which is characteristically associated with absence seizures (Cain et al., 2018).

An imbalance between excitatory (Glutamate) and inhibitory (GABA) neurotransmitters is another key factor promoting epileptiform activity. Glutamate receptors such as NMDA and AMPA become hypersensitive due to phosphorylation by kinases such as protein kinase A (PKA), protein kinase C (PKC), and Extracellular signal-Regulated Kinases 1/2 (ERK1/2), enhancing Na^+ and Ca^{2+} influx that leads to neuronal excitotoxicity (Nateri et al., 2007). Meanwhile, reduced expression of $GABA_A$ and $GABA_B$ receptors and altered receptor subunits reduce synaptic inhibitory potential and increase the imbalance between excitation and inhibition in the brain (Drexel et al., 2013).

Intracellular signaling pathways also mediate epileptogenesis and seizure activity. The mechanistic target of rapamycin (mTOR) pathway, which usually regulates cell growth and metabolism, becomes hyperactive due to mutations in genes such as Tuberous Sclerosis Complex 1 (TSC1 and TSC2) or DEP Domain Containing Protein 5 (DEPDC5) (Moloney et al., 2021). Excessive activation of mTORC1 leads to abnormal neuronal growth, disrupted neuronal migration, and increased synthesis of synaptic proteins, reinforcing hyperexcitable epileptogenic circuits (Nguyen and Bordey, 2021). Additionally, the Mitogen-Activated Protein Kinase/Extracellular signal-Regulated Kinase (MAPK/ERK) pathway contributes to the upregulation of pro-seizure genes such as Cellular-Fos (c-Fos), Brain-Derived Neurotrophic Factor (BDNF), and Early Growth Response-1 (Egr-1). Activation of ERK1/2enhances the stability of excitatory synapses and prolongs the survival of hyperactive neurons, worsening the predisposition to recurrent seizures (Alberini, 2009).

Neuroinflammation also contributes to the pathological mechanisms of epilepsy. Activation of microglia and astrocytes leads to the release of cytokines such as IL-1β, TNF-α, and IL-6, which impair blood–brain barrier integrity, modulate ion channels, and increase neuronal excitability. IL-1β, through the NF-κB signaling pathway and upregulation of COX-2, mediates a proinflammatory environment to promote seizure onset. These cytokines also reduce GABA transporter function and enhance N-methyl-D-Aspartate (NMDA) receptor expression, forming a pathological feedback for status epilepticus (Li et al., 2023).

Besides that, oxidative stress responses resulting from excessive neuronal activity lead to the accumulation of reactive oxygen species (ROS), which can damage cellular membranes and trigger neuronal apoptosis through caspase-3 activation. The imbalance between ROS production and endogenous antioxidants such as superoxide dismutase (SOD), catalase, and glutathione accelerates the degeneration of epileptogenic neurons, thereby contributing to seizure induction during epilepsy (Méndez et al., 2014).

The Role of Lactobacillus sp. as a Novel Therapy in Epileptic Seizures
Lactobacillus sp. is a group of Gram-positive, rod-shaped bacteria classified as lactic acid bacteria (LAB) due to their ability to ferment carbohydrates into lactic acid. These bacteria are facultatively anaerobic or microaerophilic, non-spore-forming, and thrive in low pH environments, making them well-suited as natural inhabitants of the human gastrointestinal tract and standard components of various fermented foods (Dempsey and Corr, 2022). Within the human body, Lactobacillus sp. contributes to maintaining gut microbiota balance, strengthening epithelial barriers, producing antimicrobial compounds such as bacteriocins and reuterin, and modulating mucosal immunity. In addition, this genus holds high value in the food and pharmaceutical industries, particularly as probiotics, which are increasingly developed as primary therapeutic agents for acute/chronic inflammation, gastrointestinal infections, metabolic disorders, and neurochemical modulation through the gut–brain axis (Ding et al., 2021; Hassan et al., 2021).

Recent genomic studies have led to a reclassification of *Lactobacillus sp.*, resulting in many species and subspecies. According to a comprehensive phylogenetic analysis conducted by Zheng et al. (2020), they reclassified 260 species into more than 25 genera. Main species commonly used in research and industry are *Lactobacillus casei* (*Lacticaseibacillus casei*), *L. helveticus, L. rhamnosus* (*Lacticaseibacillus rhamnosus*), *L. reuteri* (*Limosilactobacillus reuteri*), *L. acidophilus, L. plantarum* (*Lactiplantibacillus plantarum*), *L. salivarius, L. bulgaricus* (*L. delbrueckii subsp. bulgaricus*), *L. paracasei,* and *L. fermentum* (*Limosilactobacillus fermentum)* (Zheng et al., 2020). Due to their varying probiotic effects, these *Lactobacillus sp.* are not only pioneers in probiotics and fermentation but also promising candidates for the development of microbiota-based therapies.

Based on neuroprotective effects in the human body, several *Lactobacillus sp.* have shown favorable responses as therapeutic agents in epilepsy, particularly in managing seizures during epileptic episodes. A study by Eor et al. (2021) reported the effectiveness of a single-strain probiotic, *Lactobacillus fermentum* MSK 408, in significantly reducing seizure severity and frequency but not in the onset of seizures. Seizure scores assessed using the Racine scale showed an average score of 4 in the positive control group (induced with pentylenetetrazol, indicating tonic–clonic seizures), which decreased to a mean score of 2 in the treatment group receiving *L. fermentum* MSK 408 (indicating partial clonus of the upper body, primarily the head). The seizure frequency also dropped to zero in the treated group, compared to the positive control group with an average of more than 40 seizures (Eor et al., 2021).

Similarly, a study by Ciltas et al. (2023) reported reduced seizure activity in rats with PTZ-induced epilepsy following treatment with a probiotic combination of seven *Lactobacillus sp.* (*L. acidophilus, L. casei, L. plantarum, L. salivarius, L. rhamnosus, L. bulgaricus, and L. paracasei*) and four *Bifidobacterium sp.* (*B. lactis, B. breve, B. longum, and B. bifidum*). However, the study found no statistically significant relationship ($p > 0.05$). However, a downward trend in seizure scores and an increase in seizure onset were observed following the administration of the probiotic combination. The mean seizure score after treatment with the *Lactobacillus* and *Bifidobacterium* probiotic mix was 3 (indicating partial clonus in the bilateral forelimbs), representing a decrease compared to the positive control group, which had an average Racine score of 5 (indicative of generalized clonic seizures). Furthermore, seizure onset was delayed in the treatment group, increasing from over 50 seconds in the positive control group to over 100 seconds in the probiotic-treated group (Ciltas et al., 2023).

In another study, Kilinc et al. (2021) reported neuroprotective effects of probiotic combinations with eight *Lactobacillus* (*L. acidophilus, L. casei, L. plantarum, L. salivarius, L. rhamnosus, L. bulgaricus, and L. paracasei*) and four *Bifidobacterium sp.* (*B. lactis, B. breve, B. longum, and B. bifidum*) in PTZ-induced epileptic rats. It reported a significant increase in seizure onset time (p< 0.01), reduction in seizure duration (p<0,05), and decrease in seizure score (although not statistically significant, p> 0.05). The mean seizure (tonic-clonic) onset time increased from 90 seconds in the control group to 120 seconds in the probiotic-treated group. Seizure duration decreased from 60 seconds in the control group to <60 seconds in the treatment group. The seizure score dropped from 5 in the control group to 4 in the probiotic group, which may reflect an early neuroinflammatory and oxidative stress modulation effect (Kilinc et al., 2021).

A study by Bagheri et al. (2019) also demonstrated the effectiveness of a probiotic combination of two *Lactobacillus sp.* (L. rhamnosus and L. reuteri) and one *Bifidobacterium sp.* (*B. infantis*) administered before and after PTZ-induced seizures in rats. Seizure scores based on the Racine scale significantly decreased (p< 0.0001) from 4 in the positive control group to 2 in the pre-treatment group and 3 in the post-treatment group. These findings suggest that the probiotic combination may serve as a potential therapy to reduce seizures (Bagheri et al., 2019).

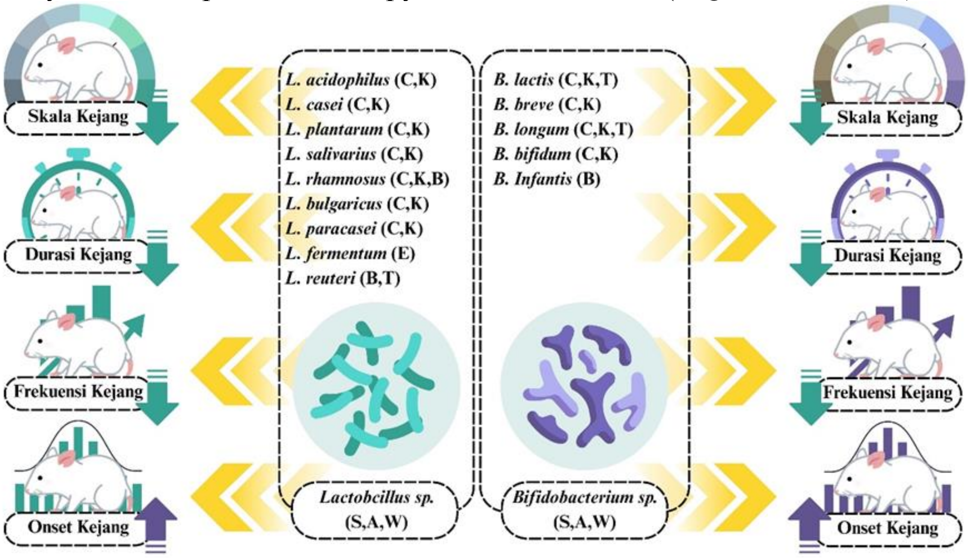

Figure 3. Role of *Lactobacillus sp.* and *Bifidobacterium sp. in epileptic seizure*.
C = Ciltas *et al.*; K = Kilinc *et al.*; B = Bagheri *et al.*; W = Wang et al.; E = Eor *et al.*; T = Tahmasebi *et al.*; A = Ali *et al.*; S = Shakoor *et al*

The Role of *Bifidobacterium sp.* as a Novel Therapy in Epileptic Seizures
Bifidobacterium sp. is a genus of Gram-positive, anaerobic, non-motile, non-spore-forming bacteria that was first isolated by Tissier in 1899 from the feces of breastfed infants. These bacteria exhibit a branched rod morphology, Y-shaped, and represent the dominant microorganisms in the infant gut, playing a critical role in the establishment of early gut microbiota (O'Callaghan and Sinderen, 2016). *Bifidobacterium* utilizes the fructose-6-phosphate phosphoketolase pathway to ferment complex carbohydrates, producing acetic and lactic acids. It allows for the metabolization of indigestible oligosaccharides, such as human milk oligosaccharides (HMOs), thereby supporting early colonization and initial development of mucosal immune function in the gut (Pokusaeva et al., 2011). Several *Bifidobacterium sp.* have demonstrated the ability to adhere to the intestinal epithelium, modulate immune responses, and are potential probiotic candidates for maintaining gut microbiota homeostasis, particularly in neuroprotective and neurodegenerative processes (Gavzy et al., 2023).

The taxonomic classification of the genus *Bifidobacterium* has evolved in parallel with advances in molecular technology. Sequence analyses of 16S rRNA and the whole genome of *Bifidobacterium sp.* have revealed *that B. infantis, B. longum, and B. suis* have genetic similarity among them, which are now categorized as a single species. B. longum is currently classified into three subspecies: *B. longum, B. infantis, and B. suis*. The species *B. breve* and *B. bifidum* play important roles in the colonization of the infant gut, with B. bifidum exhibiting strong mucosal adhesion and the ability to produce enzymes that degrade mucosal glycoproteins. Meanwhile, *B. lactis* (formerly known as *B. animalis subsp. Lactis* is recognized for its resilience in intestinal environments and is frequently used in commercial probiotic products (Dosan et al., 2024).

Tahmasebi et al. (2025) successfully demonstrated the role of *B. lactis* and *B. longum*, in combination with *L. reuteri,* in reducing seizure responses in pentylenetetrazol (PTZ)-induced epileptic rats. The study reported a significant reduction in seizure scores (Racine scale) in the treatment group receiving the probiotic combination, with a mean score of 2 compared to a mean score of 5 in the positive control group ($p< 0.05$). Additionally, the study observed a reduction in seizure duration following probiotic administration, although this was not statistically significant ($p> 0.05$) (Tahmasebi et al., 2025).

Shakoor et al. (2024) and Ali et al. (2025) also demonstrated a reduction in seizure activity in pentylenetetrazol-induced epileptic rats following administration of a probiotic combination of *Lactobacillus* and *Bifidobacterium* species. Shakoor et al. (2024) reported a significant decrease in seizure scores (Racine scale), with the treatment group receiving the probiotic combination showing a mean score of 2 (head clonus), compared to a mean score of 5 (generalized tonic-clonic seizures) in the positive control group ($p< 0.0001$). These findings were consistent with the results of Ali et al. (2025), who observed a mean seizure score of 3 (myoclonic seizures) in the probiotic-treated group, compared to a mean score of 5 in the positive control group, also statistically significant ($p< 0.0001$) (Ali et al., 2025).

Wang et al. (2022) also reported outcomes in reducing seizure scores (Racine scale) following the administration of a probiotic combination of *Lactobacillus and Bifidobacterium sp.* in kainic acid-induced epileptic rats. The mean seizure score in the positive control group was 4, which significantly decreased to a mean score of in the probiotic-treated group ($p< 0.05$). A significant reduction in seizure duration was also observed ($p< 0.01$), with the probiotic group exhibiting a mean seizure duration of less than 20 seconds, compared to over 20 seconds in the positive control group. Furthermore, seizure frequency was significantly reduced ($p< 0.01$) in the probiotic-treated group, with a mean of fewer than 10 seizures per day, compared to ≥15 seizures per day in the positive control group (Wang et al., 2022). Short-chain fatty acids (SCFAs), such as acetate and butyrate, produced by *Lactobacillus* and *Bifidobacterium sp*., are also important factors in regulating the reduction of seizure activity, including onset, duration, frequency, and severity of seizure, contributing to potential clinical improvement. It is also influenced by the modulation of inflammatory cytokine activity, oxidative stress, and neurodegenerative factors (Wlaź et al., 2024).

Regulation of Epileptic Seizure Improvement Following Probiotic Administration Through Excitatory and Inhibitory Neurotransmitter Activity

Neurotransmitters are essential chemical molecules that facilitate communication between neurons in the central nervous system. They are released from the presynaptic neuron terminals and bind to specific receptors on postsynaptic neurons, thereby modulating the electrical and biochemical activity of target cells. Neurotransmitters are classified into three major categories: excitatory, inhibitory, and modulatory. Excitatory neurotransmitters, such as Glutamate, enhance the activity of postsynaptic neurons to generate action potentials, while inhibitory neurotransmitters, such as GABA, function to suppress glutamatergic activity. Modulatory neurotransmitters, including dopamine and serotonin, influence the activity of other neurotransmitters and regulate various brain functions (Boto and Tomchik, 2019; Sheffler et al., 2025).

Glutamate is an excitatory neurotransmitter in the brain and plays a role in cognitive functions such as learning and memory. However, excessive glutamate levels can lead to excitotoxicity, neuronal damage, or death caused by overstimulation of glutamate receptors. In contrast, GABA is the primary inhibitory neurotransmitter, which helps maintain neuronal homeostasis by counteracting excessive excitatory activity. The balance between Glutamate and GABA is crucial for maintaining normal brain function, and any disruption in this equilibrium has been closely associated with the development of neurological disorders, particularly epilepsy. Increased glutamatergic activity and/or decreased GABAergic activity can lead to neuronal hyperexcitability, ultimately resulting in a seizure. Studies have shown that during status epilepticus, there is an upregulation of glutamate receptor expression and a downregulation in the number and function of GABA receptors (Sarlo and Holton, 2021).

Probiotic strains such as *Lactobacillus* and *Bifidobacterium sp*. have beneficial activity in regulating GABA/glutamate balance by increasing GABA levels and reducing glutamate concentrations in epilepsy with seizure symptoms. A study by Bagheri et al. (2019) reported a significant increase in GABA levels, with a mean concentration exceeding 0.8 ng/g in the epileptic group treated with a probiotic combination of two *Lactobacillus sp.* (L. rhamnosus and *L. reuteri*) and one *Bifidobacterium sp.* (*B. infantis*), compared to the positive control group of epileptic rats, which showed a mean GABA level below 0.7 ng/g ($p<0.01$) (Bagheri et al., 2019).

Ciltas et al. (2023) also reported an increase in GABA levels following administration of a probiotic combination comprising seven *Lactobacillus sp.* (*L. acidophilus, L. casei, L. plantarum, L. salivarius, L. rhamnosus, L. bulgaricus, and L. paracasei*) and four *Bifidobacterium sp.* (*B. lactis, B. breve, B. longum, and B. bifidum*). The treated group showed a significantly higher mean GABA level (>5 nmol/g) compared to the epileptic positive control group (<4 nmol/g, $p < 0.05$). Additionally, a reduction in glutamate levels was observed in the probiotic-treated group (mean <7 nmol/g) compared to the epileptic control group (mean >7 nmol/g), although the difference was not statistically significant ($p> 0.05$) (Ciltas et al., 2023).

A study conducted by Eor et al. (2021) further substantiates the role of *Lactobacillus sp.* in modulating GABA/glutamate balance, a crucial aspect of neuronal excitability regulation. The administration of a single probiotic strain, *Lactobacillus fermentum* MSK 408, resulted in a significant increase in GABA concentrations in epileptic seizure-induced rats, with mean levels exceeding 70 pg/mL, compared to less than 50 pg/mL in the positive control group ($p< 0.05$). Furthermore, glutamate concentrations were significantly reduced following probiotic administration, with mean values below 20 M/L, in contrast to levels greater than 20 M/L observed in the positive control group ($p< 0.05$) (Eor et al., 2021).

Studies utilizing magnetic resonance spectroscopy (MRS) have demonstrated that patients with epilepsy associated with focal cortical dysplasia (FCD) exhibit significantly elevated GABA levels in the epileptic focus compared to the contralateral region and healthy controls. This finding suggests that the increase in GABA represents an adaptive mechanism aimed at suppressing neuronal hyperexcitability in epileptogenic zones (Gong et al., 2021). This compensatory response is also reflected in the reduction of glutamate levels, which serves to decrease neuronal excitability further and prevent additional damage. Evidence indicates that in some instances of epilepsy, particularly following brain injury, glutamate levels decline as part of an adaptive process to attenuate excitatory neurotransmission (Huang et al., 2023).

CONCLUSION

Probiotic strains of Lactobacillus sp. and Bifidobacterium sp. demonstrate substantial potential as non-pharmacological alternative therapies during seizure onset in epilepsy, particularly by alleviating seizure symptoms through modulation of the gut–brain axis. Based on the reviewed studies, probiotic administration has been shown to significantly reduce frequency, duration, and severity scores of seizures, while also increasing levels of the inhibitory neurotransmitter GABA and decreasing levels of the excitatory neurotransmitter glutamate. In addition, the observed anti-inflammatory and antioxidant effects, along with improvements in blood–brain barrier integrity, further support the therapeutic benefits of probiotics in suppressing neuronal excitability and neuroinflammation, key components in the pathophysiology of epilepsy. Therefore, Lactobacillus sp. and Bifidobacterium sp. may be further developed as safe and effective innovative therapeutic approaches for preventive, curative, and adjunctive epilepsy management.

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